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LINEAR SCLERODERMA

Association With Abnormalities of the Spine and Nervous System

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CHICAGO

THE CAUSE of linear scleroderma is obscure. Several authors have been impressed by the fact that many lesions in this disease have a segmental distribution or follow the course of peripheral nerves. Therefore, they have assumed that linear scleroderma originates in the nervous system.¹ In support of the neurogenic theory are observations in cases in which the development of linear scleroderma followed nerve injury; for instance, the case of Kingery² in which, following block anesthesia of the mandibular nerve, a sclerodermatic lesion developed in the supply area of this nerve. Bettman,³ however, interpreted linear scleroderma as a developmental anomaly independent of the nervous system and rather analogous to nevi, because he observed a striking similarity in the patterns of unilateral linear nevi and linear scleroderma.

The following report is based on the observations in 13 unselected cases of linear scleroderma. All the patients were seen in the University of Chicago clinics during the fifteen year period prior to writing. Analysis of the observations in these patients will point more clearly toward the neurogenic causation of this entity.

REPORT OF CASES

For the sake of brevity the pertinent data of the cases are summarized in table form. The localization, extent and shape of lesions are repre-

From the Section of Dermatology, Department of Medicine, University of Chicago (Chief of Service, Dr. Stephen Rothman).

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sented diagrammatically, showing the spinal root zones.⁴ Description of the clinical appearance of the lesions is omitted. All lesions were clinically typical of linear scleroderma, and this diagnosis was confirmed histologically in cases 1, 2, 3, 4, 7, 11 and 13. In the following descriptions, only a few additional data are mentioned which could not be included in the table.

CASE 1—The spiral lesion on the left leg followed fairly closely what was shown by Brain⁵ and Ranson⁶ to be the border between cutaneous areas of distribution of the second and third lumbar spinal root zones. This might well represent the overlap area of these two segments. The lesion followed the course of no single cutaneous nerve, but cut across areas supplied by the lateral cutaneous nerve of the thigh and the intermediate and medial cutaneous rami of the femoral nerve, all of which originate in the lumbar plexus. Therefore, it seems that if this

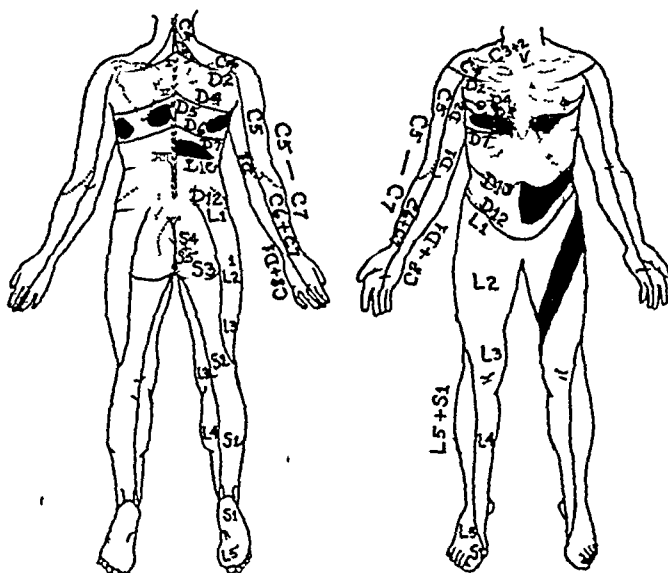


Fig. 1—Diagrams of distribution of lesions (case 1)

lesion had anything to do with the nervous system, it was of central rather than peripheral origin and its segmental spiral distribution was determined by the embryonic rotation of the lower limb bud.

The lesion on the left lower aspect of the abdomen terminated rather sharply at the midline, and its upper border, beginning medially at the umbilicus, curved as it moved laterally as is usually shown in textbooks for the border between the

4 Diagrams showing the cutaneous distribution of spinal root zones or segments and the areas of distribution of cutaneous nerves vary considerably in the works of different authors. In these case reports a simplified diagram of segmentary distribution which is used in the University of Chicago clinics was chosen on which to overlay the lesions.

5 Brain, W. R. *Diseases of the Nervous System*, ed. 2, London, Oxford University Press, 1940, p. 28.

6 Ranson, S. W. *The Anatomy of the Nervous System from the Standpoint of Development and Function*, ed. 6, Philadelphia, W. B. Saunders Company, 1939, p. 63.

ninth and tenth thoracic spinal root zones. The lesions on the chest and the back were somewhat symmetrically placed, some ran parallel to the long axis of spinal root zones.

CASE 2—The upper portion of the lesion in this case practically duplicated the lesion of the leg in the first case. However, the lower portion extended into the fourth lumbar spinal root zone. The lesion did not follow the course of any single peripheral nerve. If the origin of this lesion were in a peripheral nerve trunk, it should be expected that in the distal portion it would involve most of the cutaneous distribution of some branch of the mother nerve. If central origin is assumed, it is understandable that only a few fibers of several peripheral nerves were involved according to their spinal root origin. There was a history of mild trauma to the sacral region one and one-half years previous to the onset of the lesion.

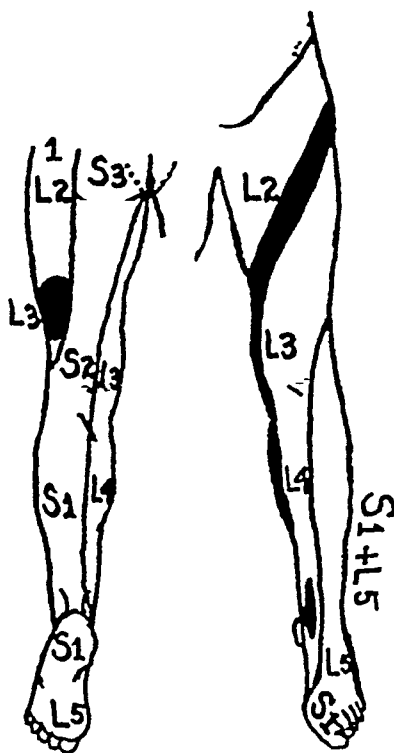


Fig 2—Diagram of distribution of lesions (case 2)

CASE 3—The distribution in the lower extremities, as seen in cases 1 and 2, was rather accurately reproduced in this case except that part of the first lumbar root zone was also involved in the inguinal region. The lesions of the shoulders and arms filled much of the zones supplied by the fourth and fifth cervical roots and involved parts of some of the upper thoracic roots. In fact, the lower borders of the lesions of the arm closely simulated the lower borders of the fifth cervical root distribution as frequently pictured. The symmetry of these lesions is striking.

CASE 4—In this case again no definite peripheral nerve distribution could be made out, but part of practically every spinal root zone from the tenth thoracic to the third sacral root zone was involved. The buttock involvement ended medially rather sharply at the lateral edge of the fourth and fifth sacral root zones, and the abdominal lesion ended at the paramedian line.

CASE 5—The lesions in this case had a distribution somewhat different from that in the previous cases. They lay within the second lumbar through the first

sacral root zones According to the diagrams of Holmes⁷ the lesions were principally in the fourth lumbar zone The abdominal lesions, which were on the opposite half of the body, were in the ninth and tenth thoracic root areas Although the lesions did not fill the area of any single peripheral nerve or its

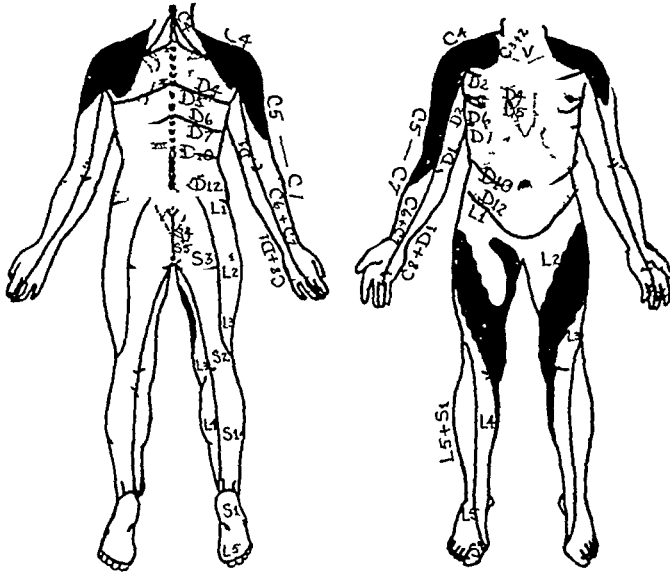


Fig 3 —Diagrams of distribution of lesions (case 3)

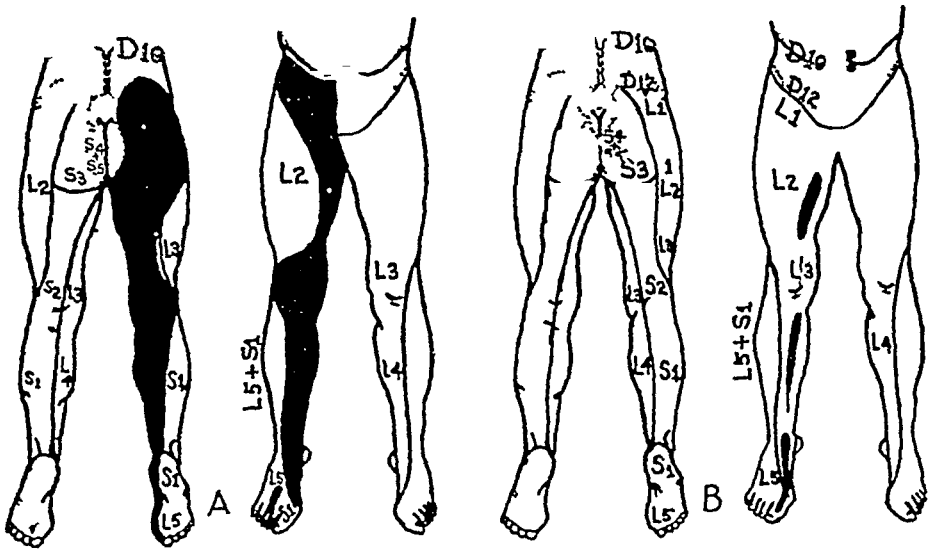


Fig 4 —Diagrams of distribution of lesions A, case 4 B, case 5

branches, it should be stated that they lay within the supply areas of the intermediate and medial cutaneous ramus and the long saphenous nerve, which are branches of the femoral nerve

7 Holmes, G Introduction to Clinical Neurology, Edinburgh, E & S Livingstone, 1916, p 75

CASE 6—The area of the lesion in this case was similar to that in the preceding one, except that it is more accurately confined to Holmes's fourth lumbar zone

CASE 7—The lesions in this case were within the second lumbar through the second sacral root zones except for the abdominal lesion, which was approximately in the ninth thoracic zone or in the overlap area of the ninth and tenth

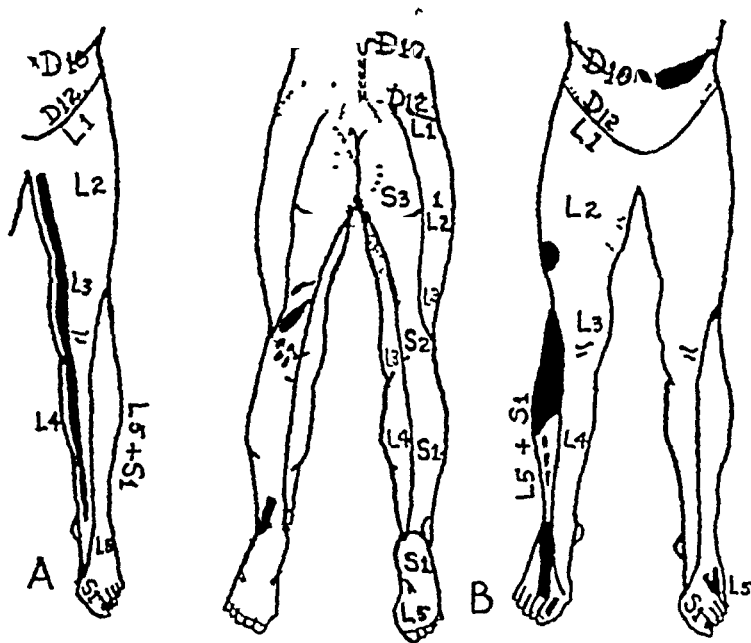


Fig 5—Diagrams of distribution of lesions A, case 6, B, case 7

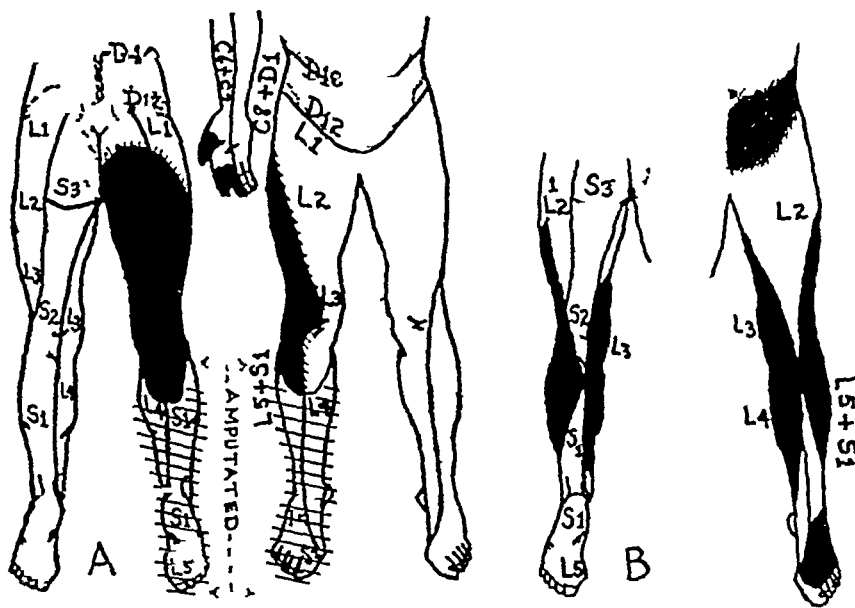


Fig 6—Diagrams of distribution of lesions A, case 8, B, case 9

thoracic zones Single nerve distributions for the lesions of the leg in this case, too, were difficult to determine

CASE 8—(The diagram is schematic and made from photographs The patient was not seen by me) When the patient was 2 years and 9 months of age limping of the right leg was first noted, and shortly thereafter shortening of this

leg, associated with hardening of the skin and muscles up to the hip, became apparent. Amputation of the right leg below the knee was done when the patient was 14 years old. During the hospitalization for amputation there was noted wasting of the first three fingers of the right hand, with the appearance of a linear scar on the third finger and contraction deformity of these fingers in flexion. Generalized weakness of the right hand and forearm was present. Talipes cavus of the left foot was also noted.

Exact outlining of the lesion of the leg could not be made. From previous description and clinical photographs after amputation, it was judged that the lesion of the leg involved the first lumbar through the fifth sacral segments. The lesion of the hand apparently involved the area of distribution of the median nerve.

CASE 9—(The diagram is schematic, made from the record and a rough drawing therein. The patient was not seen by me.) When the patient was 3 years old there was first noted an area of shiny skin about the left knee, which had increased to cover most of the leg by the time the patient was 6½ years old.

The examiner described a "defect in bodies of the second, third and fourth sacral vertebrae" and made a diagnosis of spina bifida occulta. I was unable to find this patient to get roentgenographic verification of the diagnosis.

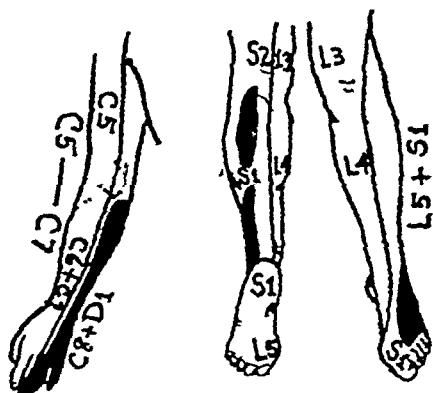


Fig. 7.—Diagram of distribution of lesions (case 10)

Several adjacent spinal root zones seemed to be involved in this case also. The absence of deep reflexes could possibly be accounted for on the basis of the contractures or muscle atrophy, but the "foot-slapping" gait indicated possible neurogenic origin.

CASE 10—At 2 years and 9 months of age the patient fell down a flight of stairs, but was apparently uninjured. A few days later swelling of the back of the left hand appeared and persisted for about two weeks, after which the skin in that region became white and glossy. This change gradually spread to the wrist and up the posterior ulnar aspect of the left forearm. At 4 years of age a similar change appeared on the superior aspect of the left foot and on the posterior aspect of the left calf. I first saw the patient when she was 8 years and 6 months of age, at which time the parents stated that the lesions had improved somewhat.

The lesion of the hand and arm, with its onset so closely following trauma and its distribution and symptoms so accurately simulating an ulnar nerve or brachial plexus syndrome, probably was due to peripheral nerve injury at the time of the fall.

The lesion of the foot and leg, beginning well over a year after the fall and not following the course of a single nerve but falling in areas of adjacent nerve roots, cannot be attributed to peripheral trauma, but was more likely due to a local pathologic condition associated with the spina bifida occulta

CASE 11—(The diagram was drawn from photographs. The patient was not seen by me.) At 38 years of age the patient first noticed thickening and wrinkling of the skin on the medial aspect of the right upper arm. Within five months the process extended in a bandlike manner and spiral path to the extent shown in the diagrams. Cordlike folds, which interfered with complete extension of the elbow, developed in the antecubital space. During the development of the lesions, transitory numbness and tingling were present in the entire right side of the body

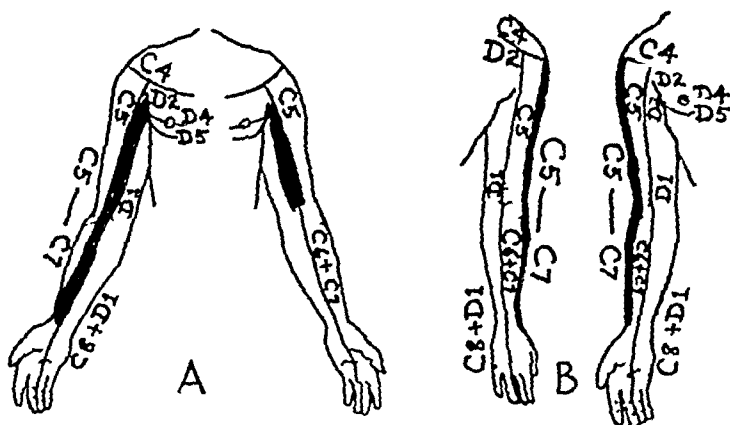


Fig 8—Diagrams of distribution of lesions A, case 11, B, case 12

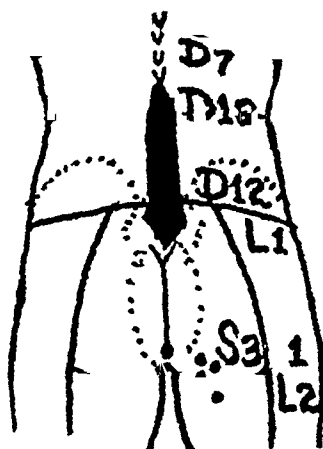


Fig 9—Diagram of distribution of lesions (case 13)

CASE 12—(The diagram is schematic. The patient was not seen by me.) The lesion did not follow the course of any peripheral nerve but lay in the fifth and sixth cervical root zones of Ranson,⁶ or fairly accurately and completely filled the fifth cervical area as mapped by Holmes.⁷

CASE 13—At 47 years of age this patient was struck by an automobile. Roentgenograms at that time showed flattening of the ninth thoracic vertebra and a questionable fracture of the right transverse process of the fourth lumbar vertebra. She recovered and was asymptomatic until the age of 50, when pruritus developed in the spinal area at about the level of the eleventh thoracic vertebra

Summary of Data in the 13 Cases Presented

Case No	Sex	Age of Onset	Sites	Röntgenologic Observations	Age Roentgenograms Taken	Spinal Root Zones Involved by Lesions	Associated Clinical Observations and Comment
1	M	20	Abdomen, back, chest and leg (bilateral with some symmetry on back and chest)	Asymmetry of laminae (S-1)	29 yr	D 5, D-6, D-7, D-9, D-10, D-11, D-12, L-2, L-3	Linear scleroderma plus morphea
2	F	4 yr 8 mo	Leg	Spina bifida occulta (S-1 and S-2)	5 yr 2 mo	L-2, L-3, L-4	
3	M	6 mo	Shoulders, arms and legs (bilateral, symmetric)	Spina bifida occulta (S-1)	8 yr 2 mo	C-4, C-5, D-2, D-3, D-4, L-1, L-2, L-3, L-4	Flexion contracture right elbow
4	F	4 yr 5 mo	Abdomen, buttock and leg	Spina bifida occulta (S-2, S-3 and S-4) Sacral part of spine normal	4 yr 9 mo 6 yr	D-10, D-11, D-12, L-1, L-2, L-3, L-4, L-5, S-1, S-2, S-3	Equinovarus deformity of homolateral foot and flexion contracture of knee, decreased volume of leg, atrophy of gluteal region, prominent veins
5	M	3 yr 6 mo	Leg, abdomen (bilateral)	Spina bifida occulta (S-1, S-2 and S-3)	7 yr 8 mo	L-2, L-3, L-4, L-5, S-1	Pes cavus of homolateral foot, muscle fibrosis, ulcer of toe right foot 2 cm shorter than left, linear scleroderma plus morphea
6	F	22	Leg	Spina bifida occulta (S-1) asymmetry of laminae, prespondylolisthesis	55 yr	L-2, L-3, L-4	Muscular atrophy of leg, prominent veins in lesion
7	F	6 yr 8 mo	Legs and abdomen (bilateral and some symmetry)	Spina bifida occulta	7 yr 10 mo	D-9, D-10, L-2, L-3, L-4, L-5, S-1, S-2	Linear scleroderma plus morphea
8	F	2 yr 9 mo	Leg and buttock	Spina bifida occulta (S-1), incomplete lumbarization of left transverse process of S-1	19 yr	L-1, L-2, L-3, L-4, L-5, S-1, S-2, S-3, S-4, S-5	Pes cavus of heterolateral foot
		14 yr	Hand	No roentgenogram of cervical part of spine		C-6, C-7	Flexion contracture and weakness of hand
9	F	3 yr	Leg and abdomen	No roentgenogram clinically spina bifida occulta (S-2, S-3 and S-4)	None examined at age of 6½ yr	D-10, D-11, D-12, L-1, L-2, L-3, L-4, L-5, S-1	Contracture deformity of homolateral knee, atrophy of leg, foot-slapping, gait, deep reflexes in leg absent

Case No	Sex	Age of Onset	Sites	Roentgenologic Observations	Age at which Roentgenograms Taken	Spinal Root Zones Involved by Lesions	Associated Clinical Observations and Comment
10	F	2 yr 9 mo	Arm	Spina bifida occulta (S-2)	4 yr 6 mo	C-8, D-1	Trauma at 2 yr 9 mo, ulnar deviation of left hand, weakness of flexion of fourth and fifth fingers, decreased volume of affected areas
			Leg	Lumbosacral part of spine normal	8 yr 6 mo	L-5 S-1	
		4 yr	Arms (bilateral symmetric)	Forked spinous processes (C-4, C-5 and C-6) osteoarthritis lower cervical part of vertebrae	38 yr	C-5 C-6, C-7, C-8, D-1, D-2	Slight flexion contraction of right elbow, paresthesias of right side
11	F	38 yr	Arms	No clinical or roentgenographic examination of the spine		C-5, C-6	Trauma at 47 yr, linear scleroderma plus morphea
12	F	6 yr	Arm	Compression fracture (L-2), flattening (T-9), fracture transverse process (L-4), osteoarthritis	47 yr 50 yr	D-10 D-11, D-12 L-1, L-2, L-3, L-4	
13	F	50 yr	Lower part of spine				

Two months later there was a pigmented and depigmented thickened scaling firm band, about 5 cm wide, extending in the midline from the tenth thoracic vertebra to the sacrum. On the right buttock were four depigmented atrophic spots, each measuring about 1 cm in diameter.

Recent roentgenograms showed a compression fracture of the body of the second lumbar vertebra, with localized osteoarthritic changes. There was minimal osteoarthritis and scoliosis of the dorsal aspect of the spine.

This patient had a midline lesion in the area of the spine following direct trauma to the spine which resulted in fractures and localized osteoarthritis. Interestingly, Pritchard⁸ presented a diagram of the cutaneous distribution of the spinal root zones which showed a central overlap of the first through the fourth lumbar over the tenth through the twelfth thoracic spinal root zones in the area of this patient's lesion.

These patients all had roentgenograms of the chest, serologic tests for syphilis, blood cell counts and urinalyses, the results of all of which were normal. In some cases tests of basal metabolism, tuberculin patch tests, serum calcium estimations and other special studies were done, and all yielded normal results.⁹

ANALYSIS OF DATA

A Localization on Lower Extremities—Analysis of the foregoing data shows that 10 of the 13 patients had lesions of one or both lower extremities. Five of these 10 patients also had lesions on the abdomen, and 2 of these showed involvement of a buttock.

None of the lesions of the leg closely followed the distribution of a peripheral nerve, but all seemed to be distributed longitudinally in the long axis of one or several spinal root zones.

Six of the 10 patients had roentgenographic evidence of varying degrees of spina bifida occulta at an age when closure of the neural arch is usually completed, and 1 patient, for whom roentgenographic examination was not done, presented clinical evidence of severe spina bifida occulta. Thus, 70 per cent of the patients with scleroderma of the legs, lower part of the abdomen or buttocks had spina bifida occulta. Two of the 3 adults in this group had definite spina bifida occulta of the first sacral vertebra. In addition, 1 showed decided asymmetry of the laminae of one sacral vertebra, another had prespondylolisthesis and a third had incomplete lumbarization of the left transverse process of the first sacral vertebra.

Seven (70 per cent) of the patients were female and 3 (30 per cent) were male.

The average age of onset in this group was 7.15 years. This figure, however, may be misleading, for 8 of the patients were under 7 years of age at the onset of the disease and 2 were 20 and 22 years of age, respectively. The average age of onset for the 8 patients under 7 years was 3.7

years. Even this average results from 7 cases in which the onset was below the age of 4 years and 8 months and 1 case in which the onset was at 6 years and 8 months. Thus, onset below the age of 5 years seems to be predominant. The significance of this early onset and the explanation of exceptionally late onset will be further elucidated in the comment.

B Localization on Upper Extremities Five of the 13 patients had lesions of one or both upper extremities. Three of these patients also had lesions elsewhere on the body. Some of the lesions of the upper extremities (cases 3, 11 and 12) were distributed parallel to the long axes of adjacent spinal root zones. However, one of the arm lesions (case 10) closely simulated the distribution and symptoms of an ulnar nerve or lower brachial plexus syndrome. In this case, the onset of the cutaneous change was preceded by trauma and the history strongly suggested that peripheral nerve injury played a role in the development of this linear scleroderma lesion. In keeping with the assumption of peripheral origin, roentgenograms of the cervical aspect of the spine showed no abnormalities in this case. In another lesion of the upper extremity (case 8) a median nerve syndrome was simulated. No history of peripheral trauma was elicited here, and roentgenograms of the cervical aspect of the spine were not available. In case 12 no clinical or roentgenographic examination of the spine was recorded. Of the remaining 2 patients with lesions of the arm, both had bilateral and remarkably symmetric lesions. In 1 (case 3), the anteroposterior and lateral views of the cervical aspect of the spine showed no abnormalities and there was no evidence of cervical ribs. In the other (case 11), the forked spinous processes of several cervical vertebrae probably were without any pathologic significance, these changes being extremely common in normal persons. On the other hand, this same patient showed some osteoarthritis of the lower cervical vertebrae, a rather uncommon observation in a person 38 years of age. Pressure effects on nerves or nervous tissue due to this hypertrophic process might well account for the symptoms.

Omitting the patient with osteoarthritis and the patient with obvious trauma, the average age of onset of the lesions of the arm was 6.8 years.

C Localization on the Midline of the Back The disease in the remaining case to be considered (case 13) was clinically and histologically typical of scleroderma. The onset was at a relatively late age, but the history of trauma was definite and the resultant abnormalities of the spine were obvious. The lesion is definitely related spatially to the overlap area of Pritchard.⁸ However, it should be stated that illustrations of other authors do not show this overlap.

⁸ Pritchard, E. A. B. *Aids to Neurology*, London, Baillière, Tindall & Cox, 1941, p. 123.

COMMENT

The diagrams indicate that in the majority of cases the lesions lay in the long axis of spinal root zones. In some cases only adjacent zones were involved, in others, however, zones were skipped, and in some lesions the relation to segmentary distribution is debatable.

More significant than the spatial distribution, for the assumption of neurogenic origin of linear scleroderma, is the high incidence of spina bifida occulta in cases with lesions of the lower extremities.

Results of studies to determine the frequency of spina bifida occulta in normal persons show wide variations. Figures for the presence of this anomaly in the fifth lumbar vertebra vary from 1.2 per cent¹⁰ to 2.3 per cent.¹¹ None in my series of 10 patients with linear scleroderma of the lower extremities showed such a defect.

Figures for the occurrence of spina bifida occulta in the combined lumbosacral aspect of the spine vary from 17.3 per cent¹² to 33 per cent,¹³ and Schmorl¹⁴ gave the results of several investigators who observed an incidence in the sacral aspect of the spine alone varying from 11 to 24 per cent. Despite these large variations, none of the figures approach the incidence of 70 per cent observed in the patients presented in this paper.

One must consider the age at which these defects are detected, for spina bifida occulta is much more frequent in young children. Hodges

9. Five of the patients described in this survey have been presented before the Chicago Dermatological Society. These case presentations and discussions have appeared in the literature as follows: Rothman, S., and Felsher, Z. Circumscribed Scleroderma, *Arch. Dermat. & Syph.* 51:77 (Jan.) 1945 (case 1); Rothman, S., and Shapiro, A. L. Linear Scleroderma, *ibid.* 53:199 (Feb.) 1946 (case 3); Rothman, S., and Krysa, H. Linear Scleroderma with Spina Bifida, *ibid.* 55:130 (Jan.) 1947; Linear Scleroderma, *ibid.*, to be published (case 7); Rothman, S., and Henningsen, A. B. Linear Scleroderma, Following the Course of Nerves, with Muscular Atrophy, *ibid.* 50:59 (July) 1944 (case 10).

10. Willis, T. A. An Analysis of Vertebral Anomalies, *Am. J. Surg.* 6:163 (Feb.) 1929.

11. Wheeler, T. Variability in the Spinal Column as Regards Defective Neural Arches, Publication 30, Carnegie Institution of Washington, 1941.

12. Bohart, W. H. Anatomic Variations and Anomalies of the Spine: Relation to Prognosis and Length of Disability, *J. A. M. A.* 92:698 (March 2) 1929; Cushway, B. C., and Maier, R. J. Routine Examinations of the Spine for Industrial Employees, *ibid.* 92:701 (March 2) 1929.

13. Roederer, C., and Lagrot, F. Le diagnostic radiologique du spina bifida occulta lombosacré, *J. de radiol. et d'électrol.* 10:255, 1926.

14. Junghanns, H. Die gesunde und kranke Wirbelsäule in Röntgenbild, in Schmorl, G. *Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern*, Leipzig, Georg Thieme, 1932, pp. 195-199.

and his co-workers¹⁵ showed the fusion of sacral arches to be normally completed during the fifth year and the order of fusion to be second, first fourth and third sacral arches, respectively. In 8 of the 9 patients with lesions of the leg of whom I have roentgenograms, the final roentgenographic study was made after they were 6 years of age. The ages at examination varied from 6 years to 55 years.

Three (cases 1, 4 and 10) of the 10 patients with linear scleroderma of the lower extremities were considered not to have spina bifida occulta. Two patients had roentgenograms made when they were between 4 and 5 years of age which showed failure of fusion of the laminae of the second sacral vertebra. Fusion was observed to be complete when a second series of roentgenograms was taken at 8 years and 6 months of age. In a strict sense, the spina bifida occulta in this case has to be regarded as physiologic. However, the observations even in these cases may be significant, because the second sacral arch is normally the first to fuse. If one regards the observation of spina bifida occulta in these patients as significant, the percentage of spina bifida occulta in this series of patients with lesions of the lower extremity increases from 70 per cent to 90 per cent.

The preceding data indicate that spina bifida occulta is significant in linear scleroderma of the lower extremities.

There has been lack of agreement as to the clinical significance of spina bifida occulta, but it has been shown that it is related to several clinical conditions. Most important of these are deformities of the feet, principally clubfoot and hollow foot. In 3 of the cases presented there was seen one or the other of these deformities of the homolateral or heterolateral foot. Paralyzes of different degrees of severity are sometimes seen with spina bifida occulta, and it should be pointed out that Money¹⁶ and others¹⁷ have reported sclerodermatous lesions occurring in patients with spinal paralyzes. Flexion contractures of the knees have also been reported to be associated with spina bifida occulta, and this was noted in 2 of my patients. In addition, 2 with lesions of the arm, showed contractures. Queyrat and his co-workers¹⁸ described trophedema of

15 Hodges, P. C., Phemister, D. B., and Brunschwig, A. *The Roentgen-Ray Diagnosis of Diseases of the Bones and Joints*, New York, Thos. Nelson & Sons, 1938, chart, p. 14.

16 Money, A. *Chronic Infantile Sclerema and Paralysis*, *Lancet* 2:811, 1888.

17 Dinkler, M. *Zur Lehre von der Sclerodermie*, *Deutsches Arch. f. klin. Med.* 48:514, 1891. Cockayne, E. A. *Congenital and Acquired Scleroderma in Childhood*, *Brit. J. Child Dis.* 13:225 (Aug.) 1916.

18 Léri, A., and Engelhard. *Trophoedème chronique et spina bifida occulta*, *Bull. et mém. Soc. d'hôp. de Paris* 44:1169 (July 30) 1920. Queyrat, Léri, A., and Engelhard. *Lésion cutanée rappelant la sclérodémie en bandes et spina bifida occulta*, *ibid.* 45:437 (March 18) 1921.

the lower extremity in a patient with spina bifida occulta and stated that the spinal defect may be an indication of "meningomedulloradicular" lesions, on which depend important "trophic" disturbances of the extremities

Obviously, spina bifida occulta in itself is not enough to cause "trophic" disturbances. However, commonly the osseous anomaly is associated with pathologic conditions of the meninges and the cord. The observations of von Recklinghausen,¹⁹ and more recently of Christopher²⁰ and Brickner,²¹ indicate that in spina bifida occulta the nerve fibers of the cauda equina may be adherent to the superficial structures or that there may be pressure on the cord at the point of the spinal defect. Brickner enumerated the following various conditions which may accompany spina bifida occulta and cause remote neuromuscular symptoms: a distinct meningocele protruding through the bony cleft, a closure of the cleft by a tough membrane adherent to the skin, the perforation of the membrane by a dense band attached to the subcutaneous tissue externally and compressing the cord structures internally, fat tissue lying within the canal concealed by this membrane, a bulging of the dura mater, an exostosis within the canal compressing the cord structures and a myofibrolipoma extending through the cleft into the bony canal and compressing the cord and its roots or causing a degeneration of the cord tracts themselves. If one realizes the great variety of these associated phenomena, it becomes understandable that in some cases spina bifida occulta will not cause demonstrable pathologic changes, whereas in other cases it will be associated with severe "trophic" disturbances. The type, localization and extent of the lesion of the cord or spinal root will determine the type, localization, extent and unilaterality or symmetry of the "trophic" lesions.

A possibly important mechanical factor in the development of "trophic" disturbances is the differential rate of growth of the spinal column and the spinal cord. In early intrauterine life, the cord fills the canal and the nerve roots emerge from the canal horizontally, whereas in adult life, the cord is only two thirds as long as the canal and the nerve roots have necessarily lengthened. According to Caffey,²² the rate of lengthening of the spinal column is greatest during the first two

19 von Recklinghausen, F. Untersuchungen über die Spina bifida, *Archiv f. path. Anat.* 105:243, 1886.

20 Christopher, F. Spina Bifida Occulta, with Report of 1 Case, *Internat. Abstr. Surg.* 33:1 (July) 1921.

21 Brickner, W. M. Spina Bifida Occulta, *Am. J. M. Sc.* 155:473 (April) 1918.

22 Caffey, J. Pediatric X-Ray Diagnosis. A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology, Chicago, The Year Book Publishers, Inc., 1945, p. 784.

years and the increase is greatest in the lumbar aspect of the spine. In case of developmental anomalies as previously listed, abnormal tension on nervous structures will be greatest during the first two years. Allowing some time for the development of "trophic" changes, this fact seems to be in keeping with the early age of onset of linear scleroderma. On the other hand, the final length of the spine is not attained until between the twenty-second and the twenty-fourth year, which explains the cases in which the disease started not in early childhood but at ages 20 (case 1) and 22 (case 6). The cases in which the disease started later than this could be explained by either trauma (case 13) or osteoarthritis (case 11).

In the preceding discussion the word "trophic" was in quotation marks because the foundation of this concept is still obscure. Clinical experience leaves little doubt that lesions of the nervous system cause disturbances in the normal development and nutrition of tissues in the supply area. Perforating ulcers and neurogenic arthropathy (Charcot joint) in tabes and ulcers in syringomyelia are striking examples of this kind of disorder, and several authors²³ have described other manifestations which had to be interpreted as trophic disturbances. However, the study of nervous influence on tissue nutrition has not elucidated the intimate nature of this influence. Whether there is a special system of trophic fibers or whether trophic impulses are efferent ("antidromic") impulses traveling in posterior root fibers, and whether the nerve effect on tissues is direct or secondary through the effect of nervous impulses on blood vessels, has not been definitely established.

There is a remarkable similarity between single features reported to be trophic in diseases of the nervous system and features of scleroderma. In both instances, the epidermis may be thin, smooth, shiny and devoid of wrinkles or it may exhibit hyperkeratosis, scaling and wrinkling. There is usually loss of elasticity. Changes in color due to either hyperpigmentation or depigmentation are frequent. Anhidrosis is more frequent, but hyperhidrosis sometimes occurs. I have seen a patient with a single patch of morphea whose initial complaint was localized hyperhidrosis in the area, but when the cutaneous changes developed more fully there was decreased sweating in this area. Both cyanosis and hyperemia have been described, and visible prominence of veins has been noted. Ulceration of the skin is likely to occur where it is subjected to continued pressure.

²³ Livingston, W. K. *Pain Mechanisms: A Physiologic Interpretation of Causalgia and Its Related States*, New York, The Macmillan Company, 1943, p. 103. Pollock, L. J., and Davis, L. *Peripheral Nerve Injuries*, New York, Paul B. Hoeber, Inc., 1933, ed. 1, pp. 155 and 156. Brain, W. R. *Diseases of the Nervous System*, ed. 2, London, Oxford University Press, 1940, p. 646. Wilson, S. A. K. *Neurology*, edited by J. N. Bruce, Baltimore, Williams & Wilkins Company, 1940, vol. 2, p. 1400.

The deeper structures, too, are involved. The subcutaneous tissue may undergo hypertrophy followed by atrophy and feels hard and inelastic. In some cases the skin is thrown into folds. Because of muscle atrophy there may be decreased volume of the extremity, and the muscles may undergo fibrous changes with consequent decreased mobility, thus contributing to contracture deformities. All these features have been noted in 1 or more of the patients described in this paper, as well as in patients with trophic disturbances following frank lesions of the nervous system.

This clinical resemblance, together with the fact that spina bifida occulta and other abnormalities of the spine seem to be extremely common in patients with linear scleroderma, indicates that the tissue changes in linear scleroderma originate in lesions of the nervous system. In the majority of cases the responsible lesion seems to be localized in the central nervous system or spinal roots and is caused by either developmental anomaly or osteoarthritis. Exceptionally, however, the disease may originate in peripheral nerve lesions following trauma.

It is remarkable that in cases 1, 2 and 3 the arrangement and shape of the lesion on the left thigh are prototypically identical. Because of individual variations of segmentary distribution, it is difficult to evaluate this observation. However, as previously mentioned, according to the diagrams in the works of Brain⁵ and Ranson⁶ this band corresponds to the boundary of the second and third lumbar zones and may possibly be an overlap area in some persons. This observation, together with the possible relation of the lesion in case 13 to an overlap area, somewhat suggests that overlap may play some role in the development of linear scleroderma. One may speculate that trophic disturbances in overlap areas are "irritative" in nature rather than due to functional deficiency of nervous impulses for localization in overlap areas necessarily means summation of some disturbance, and summation is conceivable only in cases of "irritative" disturbances.

The possibilities for roentgenologic study of linear scleroderma have not been exhausted in this presentation. Willis²⁴ has shown that interruptions in continuity occur oftener in lateral portions of the neural arch than in the central portion. These lateral defects cannot be seen in anteroposterior and lateral views as employed in this survey but require special oblique views which might in some cases explain the unilateral localization of the scleroderma lesion on the side of the bony defect. Also, roentgenograms made after subdural injections of a shadow-casting substance may demonstrate the evidence of cord pressure and locate the point of compression when it is present in spina bifida occulta thus

24: Willis, T. A. Backache from Vertebral Anomaly, Surg., Gynec. & Obst. 38: 638 (April) 1924.

providing the possibility of surgical treatment and prevention of progression of the scleroderma

OTHER FORMS OF SCLERODERMA

This study was restricted arbitrarily to linear scleroderma occurring on the trunk and extremities. A similar study of linear scleroderma of the head ("en coup de sabre") is being prepared with particular reference to its relation to facial hemiatrophy. Recently, Wartenberg,²⁵ in his study on facial hemiatrophy and scleroderma "en coup de sabre," concluded that the latter represents abortive progressive facial hemiatrophy and that both conditions can be interpreted as being due to degenerative processes in the nervous system. My data support this view.

Because of great similarity of the tissue changes in the different forms of scleroderma, the possibility must be considered that morphea and diffuse progressive scleroderma may also represent neurogenic trophic disturbances similar to linear scleroderma.

Concerning morphea, there were combinations of linear scleroderma and morphea in 4 of the patients presented here. In case 1, although most lesions of the trunk followed the long axis of spinal root zones, others did not, and the round lesions among them could be considered morphea. Observations in roentgenograms of the cervical and thoracic aspects of the spine in that case were normal. A similar situation with abdominal lesions was encountered in case 5. In case 7 the patient had many round lesions on the thigh typical of morphea on an extremity involved with linear scleroderma. In case 13 there were four round discrete lesions of morphea on a buttock in addition to the linear lesion on the midline of the back. Furthermore, a patient with scleroderma "en coup de sabre" had typical morphea of the trunk. These combinations strongly suggest identical pathogenesis of linear scleroderma and morphea. On the other hand, it should be pointed out that linear scleroderma is characterized by (1) relatively early onset, (2) frequent occurrence of spina bifida occulta and (3) atrophy involving deep structures. In cases of morphea only, these characteristics are absent. The average age of onset in 20 unselected cases of morphea seen in this department was 28.8 years. The atrophic process did not involve muscle and bone in any of them. Finally, in connection with this study, roentgenographic examination of the spine was done in 6 patients with morphea only. Five showed no abnormalities of the spine which could be related to morphea, and only 1 patient, 69 years of age, showed severe osteoarthritis with osteophyte formation.

Thus, the available data are insufficient to decide whether linear scleroderma and morphea are related conditions, but the possibility that morphea is also of trophic origin cannot be excluded.

²⁵ Wartenberg, R. Progressive Facial Hemiatrophy, *Arch Neurol & Psychiat* 54:75 (Aug.) 1945

Even less is known of the relationship between the circumscribed forms and diffuse progressive scleroderma. Some evidence for the neurogenic basis of the generalized form was furnished by Rake²⁶

SUMMARY AND CONCLUSIONS

The histories and diagrams of lesions of 13 patients with linear scleroderma revealed that in the majority of cases the lesions lay in the long axis of spinal root zones and less frequently followed the distribution of peripheral nerves.

Seventy per cent of the patients with scleroderma of the legs, lower part of the abdomen or buttocks had spina bifida occulta, and some had other abnormalities of the lower part of the spine in addition. One patient with lesions of the arm had localized cervical osteoarthritis, and 1 with a lesion on the midline of the back had localized changes of the lower thoracic and lumbar aspects of the spine following trauma. In 1 patient the lesion developed after an injury and followed the course of a peripheral nerve.

Spina bifida occulta is sometimes associated with other local pathologic conditions which affect the nervous system. In linear scleroderma, these conditions plus the normal differential rate of growth of the spinal cord and spinal canal could determine the usual early onset of lesions of the leg, which in this series was 3-7 years.

Scleroderma has many characteristics typical of trophic disturbances associated with frank lesions of the nervous system, and all forms of scleroderma show similar tissue changes. Four of the patients had both morphea and linear scleroderma, which suggests a common pathogenesis for these entities. However, the relation of the two diseases requires further study.

Roentgenographic studies following injection of radiopaque substance intradurally may furnish evidence indicating surgical treatment to prevent progression of linear scleroderma of the legs.

The spatial distribution of lesions, the high incidence of demonstrable lesions of the spine in patients with linear scleroderma and the similarity of these lesions to trophic disturbances suggest that this disease originates from lesions in the nervous system.

NOTE Since the completion of this manuscript the presentation of case 6 and its discussion have been published (*ARCH DERMAT & SYPH* 57:447 [March] 1948). H. Haxthausen (*Acta dermat-venereol* 27:352, 1947) reported transplantation experiments the results of which led to the conclusion that morphea is a disease of trophic-neurotic origin.

Dr. Stephen Rothman gave suggestions in this work and in the preparation of the manuscript.

26. Rake, G. On the Pathology and Pathogenesis of Scleroderma, *Bull Johns Hopkins Hosp* 18:212 (April) 1931.

EXTERNAL USE OF "CARBITOL SOLVENT," "CARBITOL" AND OTHER AGENTS

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"CARBITOL solvent" (monoethyl ether of diethylene glycol) is of interest in dermatology because it is an ingredient of many commercial cosmetic products and of certain formulas recommended for use on the skin. It is said to confer a "vanishing effect," which appears to be esteemed in these preparations. This effect suggests that "carbitol" may be absorbed from the skin. If so, its use might be injurious, especially to the kidneys, which are readily damaged by members of the ethylene series of glycols.

In fact, von Oettingen and Jirouch,¹ Laug, Calvery, Morris and Woodard,² Kesten, Mulinos and Pomerantz³ and Hanzlik and his collaborators⁴ have demonstrated renal and hepatic damage in various ani-

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1 von Oettingen, W. R., and Jirouch, E. A. The Pharmacology of Ethylene Glycol and Some of Its Derivatives in Relation to Their Chemical Constitution and Physical Chemical Properties, *J. Pharmacol. & Exper. Therap.* **42**: 355, 1931.

2 Laug, E. P., Calvery, H. O., Morris, H. J., and Woodard, G. The Toxicology of Some Glycols and Derivatives, *J. Indust. Hyg. & Toxicol.* **21**: 173, 1939.

3 Kesten, H. D., Mulinos, M. G., and Pomerantz, L. Pathologic Effects of Certain Glycols and Related Compounds, *Arch. Path.* **27**: 447 (March) 1939.

4 (a) Hanzlik, P. J., Lawrence, W. S., and Laqueur, G. L. Comparative Chronic Toxicity of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Related Glycols. Results of Continued Drinking and Feeding, *J. Indust. Hyg. & Toxicol.* **29**: 233, 1947. (b) Hanzlik, P. J., Luduena, F. P., Lawrence, W. S., and Hanzlik, H. Acute Toxicity and General Systemic Actions of Diethylene Glycol Monoethyl Ether (Carbitol), *ibid.* **29**: 190, 1947. (c) Hanzlik, P. J., Lawrence, W. S., Fellows, J. K., Luduena, F. P., and Laqueur, G. L. Epidermal Application of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols. Absorption, Toxicity and Visceral Damage, *ibid.* **29**: 325, 1947. (d) Luduena, F. P., Lawrence, W. S., Fellows, J. K., Clark, W. H., and Hanzlik, P. J. Excretion and Fate of Diethylene Glycol Monoethyl Ether (Carbitol) After Epidermal and Other Methods of Administration, *Arch. internat. de pharmacodyn. et de therap.* **75**: 1, 1947.

mals following ingestion, injection and external application of "carbitol" and "carbitol solvent" Largely for this reason, these products have been prohibited for internal administration In view of the extensive use of "carbitol"-containing products by the public, it is surprising to find only one clinical report⁵ on the possible hazards in the use of these products on human skin

My interest in "carbitol solvent," or "carbitol," was especially aroused when its topical application in small amounts was observed to produce fatalities in rabbits, with great regularity⁴ It was then being synthesized and delivered to cosmetics manufacturers on a large scale The "carbitol" content ranged from 5 to 50 per cent in shampoos and shaving, cleansing, cold, vanishing and other creams used in unknown amounts by a considerable proportion of the population Workers in several large industries were exposed to contact with this chemical It obviously was not as immediately fatal in human beings as in animals, but it seemed important to investigate its possible local and systemic effects in human beings The results obtained are briefly presented in this paper

A short description of the products used is first in order, particularly as the terminology in the literature is somewhat confusing Monoethyl ether of diethylene glycol is the chemical name for "carbitol," a practically pure compound containing not more than 0.2 per cent of ethylene glycol The commercial grade is generally referred to as "carbitol solvent" or "technical carbitol" and is a mixture of 70 per cent "carbitol" and 30 per cent ethylene glycol It has been widely used for years as a solvent or vehicle in dye, lacquer and cosmetic industries⁶ In cosmetics a content of not more than 5 per cent is permitted by the Food and Drug Act

Since "carbitol" is more uniformly absorbed from the skin of animals than ethylene glycol⁴ and since it is the principal component in "carbitol solvent," considerable interest is attached to it Its properties are rather interesting

"Carbitol" is a clear colorless liquid with a mild pleasant odor It has a high boiling point (201.9 C) and is only slightly hygroscopic It definitely retards the drying of ointments When dyes are incorporated, their intensity and spreading power are increased, giving the resulting preparation a more uniform color It is also an excellent solvent for most perfumes "Carbitol" is water soluble and a mutual solvent for

5 Cranch, A. C., Smyth, H. F., Jr., and Carpenter, C. P. External Contact with Monoethyl Ether of Diethylene Glycol (Carbitol Solvent), *Arch. Dermat. & Syph.* 45:533 (March) 1942

6 Emulsions, ed. 7, New York, Carbide and Carbon Chemicals Corporation, 1946

soaps, oils and waxes, correcting immiscibility and forming finer dispersions in water. It has a soothing softening effect on the skin and does not have the stickiness or slight burning sensation encountered with solvents containing glycerin. A similar emollient effect is noticeable in lotions after addition of 5 per cent "carbitol." It is difficult to incorporate more than 20 per cent "carbitol" in an ointment, and use of more than 5 per cent appears unnecessary. The results described first are those of patch tests in which certain glycols were used as controls for "carbitol solvent" and "carbitol."

TABLE 1—*Results of Patch Tests with Undiluted "Carbitol Solvent" and Propylene Glycol*

Substance	Number of Patients	Positive Results	Negative Results
"Carbitol solvent"	99	24	75
Propylene glycol	99	17	82

PATCH TESTS WITH "CARBITOL SOLVENT," "CARBITOL" AND SOME GLYCOLS

Undiluted "carbitol solvent" and propylene glycol patch tests were applied to 99 patients in the Stanford Skin Clinic. Muslin squares were saturated with the test solution, covered with a larger piece of "cellophane" and then secured with elastic adhesive or "scotch" tape. They

TABLE 2—*Results of Patch Tests with Undiluted "Carbitol Solvent" and Propylene Glycol Repeated Four Weeks After the Initial Test**

	Positive	Negative	Positive	Negative
"Carbitol solvent"	9	4	6	26
Propylene glycol	7	6	4	28

*In the initial patch test results were positive in 13 persons (1 of whom had a negative reaction to propylene glycol) and negative in 32.

were removed after forty-eight hours and the sites inspected again at ninety-six hours and weekly thereafter for one month.

The results obtained with "carbitol solvent" and propylene glycol in 45 patients, who returned for repeat patch tests four weeks later, are given in table 2.

The result was not entirely in agreement with the previous response in each person, but this probably only reflects the difficulty encountered

in deciding whether or not a reaction was positive. No strongly positive reactions were seen, suggesting, in this small group, that the sensitizing powers of "carbitol solvent" and propylene glycol are not great.

Patch tests were then done on 31 additional patients, using aqueous dilutions of "carbitol," "carbitol solvent" and several glycols, as indicated in table 3. All of the positive reactions in tables 1, 2 and 3 consisted merely of faint erythema, restricted to the area tested and persisting at least forty-eight hours after removal of the patch. Persistent erythema was also noted in rabbits after epidermal applications, and cutaneous sections showed a mild lymphocytic infiltration of the corium.⁴ Apparently, this erythema represents a mild irritant effect, rather than sensitization, and is not specific, since it occurred with all agents, regardless of chemical composition. There were no positive reactions to 5 per cent concentrations of any of the substances tested, and to the 10 per cent group

TABLE 3 — *Positive Reactions to Patch Tests with "Carbitol" and Some Glycols in 31 Additional Patients*

	No. of Patients with Positive Reactions to the Concentrations Used				
	100 Per Cent Concentrations ^a	50 Per Cent Concentrations ^a	25 Per Cent Concentrations ^a	10 Per Cent Concentrations ^a	5 Per Cent Concentrations ^a
Carbitol solvent	14	11	2	1	0
Ethylene glycol	12	8	5	1	0
Propylene glycol	11	9	1	0	0
Diethylene glycol	4	2	1	0	0
Carbitol	5	3	1	0	0

^aAqueous

only one reaction to "carbitol solvent" and one to ethylene glycol occurred. Perhaps the true incidence of reactions to patch tests is indicated by the residual scaling seen in thirteen undiluted "carbitol solvent," and ten propylene glycol, sites and the hyperpigmentation which occurred in 3 patients of each of these groups.

The age, sex, race, type of skin, complexion, history of cutaneous sensitivity, atopy and diagnostic factors were unimportant in the incidence of reactions. In no instance was a strongly positive reaction to a patch test seen in dermatitis due to cosmetic contact.

These results with "carbitol solvent" differ somewhat from those of Cranch Smyth and Carpenter,⁵ who reported "definite reactions" to "carbitol solvent" in only 7 of 98 patients. Their wording suggests that they encountered additional indefinite reactions. In their series, the initial period of contact was seven days, and after a ten day interval the same areas were retested for three days. Sixty persons gently rubbed the

"carbitol solvent" on one wrist and glycerin on the other for five minutes on ten consecutive days, leaving the areas unwashed for one hour. Seven patients had positive reactions, consisting of mild dermatitis of the entire area. Most patients reported transient congestion from both materials, so that the mild irritation was not specific for "carbitol solvent." Cranch, Smyth and Carpenter also compared the irritant effects of "carbitol solvent" and glycerin on the rabbit conjunctiva and observed them to be slight. These materials, in 50 per cent and 70 per cent concentrations, were applied to rabbit wounds of different sizes and depths, without demonstrable delay in healing or injury from absorption.

Maynard⁷ tested 225 patients with undiluted "carbitol solvent," "carbitol" and dilutions in "carbowax" and ethyl alcohol. Using adequate controls, he observed only four mildly positive reactions in the entire group.

GENERAL EFFECTS FROM EXTERNAL APPLICATIONS OF "CARBITOL SOLVENT" AND "CARBITOL" IN DERMATOLOGIC FORMULAS

One formula containing "carbitol" (polyethylene glycol) was found in the dermatologic literature. Reuter⁸ advised prophylactic application of a vanishing cream containing 9 per cent "carbitol" for the protection of hosiery workers who handled silk soaked in a highly alkaline solution. This preparation was also recommended by Anderson⁹ in two noteworthy contributions to clarity in diagnosis and treatment of industrial dermatoses.

"Carbitol solvent" was used in 55 ambulatory patients and "carbitol" in 9. Mixtures of from 5 per cent to 50 per cent "carbitol solvent" were prescribed in water, calamine lotion N F, compound starch lotion, rose water ointment U S P and a proprietary product containing cholesterolized wool fat base.¹⁰ The diagnosis and the person largely determined the vehicle employed, as well as the extent, frequency and total period of application. Routine instructions were to apply the medicament to the entire body, or to the affected parts, three or more times daily. The duration of treatment ranged from one to twelve weeks. Twenty-six patients, or 40 per cent, were treated for contact dermatitis,

⁷ Maynard, M. T. R. Personal communication to the author.

⁸ Reuter, M. J. Prevention of Industrial Dermatitis, *Indust Med* 10 147, 1941.

⁹ Anderson, N. P. Contact Dermatitis with Special Reference to Industrial Dermatitis, *Indust Med* 12 584, 1943, *New Concepts in the Therapy of Industrial Contact Dermatitis*, California & West Med 62 17, 1945.

¹⁰ The trade name of this product is "aquaphor," and it is said to contain "complex high molecular hydroxyl animal fat compounds readily binding water incorporated in indifferent aliphatic hydrocarbons and absorbing at least three times its own weight of water or aqueous solutions of medicaments."

with the diseases in the balance of the patients fairly evenly distributed among other common dermatoses. The vehicle, average weeks of use and estimated amount of "carbitol solvent" applied, for the entire group, are shown in table 4. The same formulas containing "carbitol" had been used in rabbits by Hanzlik and his co-workers⁴ and did not appear to hinder absorption of the "carbitol," since there was a rate of mortality of 50 per cent in these animals following thirty daily applications of 0.32 cc per kilogram of body weight, equivalent to a total of 156.8 cc per week in a human being of 70 Kg. The average survival period was twenty-six days.

The largest total amount of "carbitol solvent" applied by any patient was 648 cc. This was used over a period of nine weeks, averaging 72 cc per week. The largest weekly application was 180 cc for two weeks.

TABLE 4—*Topical Use of "Carbitol Solvent" in Different Vehicles*

Number of Patients	Vehicle	Period of Application (Weeks)	'Carbitol Solvent (Cc per Week)
5	Water	6.2	52.0
5	Calamine lotion N.F.	2.8	16.0
28	Compound starch lotion*	3.2	33.0
5	Cold cream U.S.P.	1.6	23.0
21	Aquaphor '10	2.3	27.0

*The composition of compound starch lotion was as follows: zinc oxide 10 per cent, starch 10 per cent, glycerin 1 per cent, and lime water enough to make 100 per cent.

Repeated questioning and examination revealed no symptoms or signs of toxicity in any of the 64 patients. Three mild exacerbations of the presenting dermatosis occurred and may have been due to "carbitol solvent," although this was not proved. Urinalysis, complete blood cell count and blood urea, phenosulfonphthalein and cephalin-cholesterol flocculation tests were done before, and at various intervals after the application of "carbitol solvent" in one third of the patients, and some of these tests were done in a number of others, but no injurious effects were demonstrable by these methods.

EXCRETION OF MONOETHYL ETHER OF DIETHYLENE GLYCOL AND GLUCURONIC ACID

The urinary excretion of monoethyl ether of diethylene glycol was determined in twenty-four hour specimens of urine from 9 patients according to a distillation method developed by Luduena and his co-workers⁴ and by direct titration for oxidizable material in urinary fil-

trates¹¹ Table 5 shows the total and weekly amounts of "carbitol solvent" and "carbitol" applied, which were fairly representative of the entire group. No definite excretion was observed, nor was diethylene glycol monoethyl ether xanthate demonstrable in thirteen specimens of urine from 3 patients. Deichmann's method was utilized for estimating the

TABLE 5—Urinary Excretion of Monoethyl Ether of Diethylene Glycol and Glucuronic Acid After External Application of "Carbitol Solvent" and "Carbitol"

Patient	Sex	Total "Carbitol" Applied (Gm)	Period of Application (Weeks)	"Carbitol" (Cc. per Week)	Vehicle	Number of 24 Hour Specimens of Urine Examined for			
						DEGM (by Distillation)	Glucuronic Acid	DEGM Xanthate	Follow up (Mo.)
Tr	♂	510	12	42.5	Water	4	2	—	—
		120	8	15.0	Water	5	—	5	24
Dy	♂	345†	12	29.0	Water and "Aquaphor" ¹⁰	4	4	4	16
Co	♀	180	2	90.0	Compound starch lotion	1	1	—	5
Sn	♂	60†	2	30.0	"Aquaphor"	1	1	—	12
Bn	♂	48	3	16.0	"Aquaphor"	4	4	4	45
Yg	♀	48†	4	12.0	"Aquaphor"	1	1	—	12
As	♂	12†	2	6.0	"Aquaphor"	1	3	—	2

*DEGM is monoethyl ether of diethylene glycol

†Three specimens of urine from 2 other patients not in the table were examined, with negative results, the total was twenty-four specimens of urine

‡These patients received mixtures containing "carbitol," all others receiving mixtures containing "carbitol solvent"

level of urinary glucuronic acid, a conjugate of diethylene glycol monoethyl ether, with negative results in sixteen specimens of urine from 7 patients. These negative results for glucuronic acid complemented those for monoethyl ether of diethylene glycol in human specimens of urine and, in turn, agreed with the essentially negative results in rabbits.¹²

SUMMARY AND CONCLUSIONS

Patch tests indicate that monoethyl ether of diethylene glycol does not possess high sensitizing powers for human skin and is probably seldom responsible for contact dermatitis from cosmetics.

11 The determinations of the monoethyl ether of diethylene glycol and glucuronic acid and isolation of the xanthate were made by Dr. F. P. Luduena and Miss Jean K. Fellows of the Stanford Department of Pharmacology and Therapeutics.

12 Fellows, J. K., Luduena, F. P., and Hanzlik, P. J. Glucuronic Acid Excretion After Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols, *J. Pharmacol. & Exper. Therap.* 89:210, 1947.

“Carbitol solvent” and “carbitol” appear innocuous when applied externally in lotions and ointments, even in rather high concentrations used over a considerable period of time

Absorption in human beings is not demonstrable, and is apparently negligible, when “carbitol solvent” or “carbitol” is applied in amounts greater than would be reasonably expected in the routine application of cosmetics

It is believed that the addition of “carbitol” to certain prescriptions for lotions and ointments will improve them by making them more uniform in consistency, by retarding drying and by enhancing their emollient effect

TINEA CAPITIS

Due to Combined Infection With *Microsporum Audouinii* and *Microsporum Lanosum*,
Report of a Case

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COMBINED infections with fungi of various types are rarely reported. Muskatblit¹ in 1941 reviewed 36 cases in the literature and put on record 6 cases of his own, the patients having been observed during a period of ten years. He² added another case to this list in 1946. Lewis and Hopper³ in 1943 presented the histories and critical evaluation of 23 cases of combined, consecutive and concurrent fungous infections⁴ among 1 200 persons suspected of having a fungous disease. Sabouraud⁵ observed an undetermined number of combined infections of the scalp with *Trichophyton crateriforme* and a microsporum.

With the exception of Sabouraud's observations, the aforementioned 66 cases include involvement of one or several sites of the human skin and its appendages with two or more different fungi. The scalp was the site of a combined infection in only 19 of these 66 cases (table 1). Eight different fungous associations occurred on the scalp (table 2). Lombardo did not mention the specific trichophyta isolated in his cases of combined favus and trichophytosis. The assignment of this group to one of the other

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1 Muskatblit, E. Combined Fungous Infections. Report of Six Cases with a Review of Thirty-Six Cases from the Literature, *Arch. Dermat. & Syph.* 44: 631 (Oct.) 1941.

2 Muskatblit, E. Dermatophytosis Due to Combined Infection with *Trichophyton Interdigitale* and *Trichophyton Purpureum*. Report of a Case, *Arch. Dermat. & Syph.* 54: 558 (Nov.) 1946.

3 Lewis, G. M., and Hopper, M. E. Concurrent, Combined and Consecutive Fungous Infections of the Skin. Cultural Experiences, *Arch. Dermat. & Syph.* 47: 27 (Jan.) 1943.

4 Lewis and Hopper used the term "consecutive" in instances of fungous infection due to one pathogen followed by a second fungous infection due to a species different from the first. "Concurrent" denoted infection with two or more different organisms, at different sites, without causative relation. The term "combined" was reserved for infections with two or more fungi isolated from the same site.

5 Sabouraud, R. *Les teignes*, Paris, Masson & Cie, 1910.

TABLE 1 — *Combined Fungous Infection of the Scalp, Reported in the Literature*

Author	(Date)	Number of Cases	Causative Fungi	Comment
Aubert (Lyon méd 22 583 1876)		2*	T violaceum and T schoenleini	=
Bodin (Ann de dermat et syph 1 327 1910)		1*	T violaceum and T schoenleini	
Barbaglia (Gior ital di mal ven 49 911 1914)		1	T violaceum and T cerebriforme	
Brault and Viguiet (Ann de dermat et syph 6 169 1916)		1	T violaceum and T schoenleini	
Finkelstein and Sigalova (Samprosvet Guvzdrava 1925)		1	T violaceum and M sp †	*
Lombardo (Gior ital di dermat e sif 67 258 1926)		3	T sp † and T schoenleini	* Mentioned
Karrenberg (Arch Dermat & Syph 17 519 [April] 1928)		1	E inguinale and T purpureum‡	*Described as E rubrum like fungus
Karrenberg (Arch f Dermat u Syph 154 668, 1928)		1	T niveum§ and T cerebriforme	
Tschernogubow and Muskatblit (Arch f Dermat u Syph 159 46 1929)		3	T violaceum and T schoenleini	
Tschernogubow and Muskatblit (Arch f Dermat u Syph 159 46 1929)		3	T crateriforme and T schoenleini	
Tschernogubow and Muskatblit ¹⁴ (Arch f Dermat u Syph 159 46 1929)		1	M lanosum and T schoenleini	
Muskatblit ¹	(1941)	1	T violaceum and T schoenleini	

*No culture methods employed

†Species not identified

‡Described as *Epidermophyton rubrum*-like fungus§Described as *Trichophyton niveum denticulatum*TABLE 2 — *Reports in the Literature of Fungous Combinations and Their Relative Frequency of Occurrence*

Fungous Combinations	Number of Cases
T violaceum and T schoenleini	8*
T sp † and T schoenleini	3
T crateriforme and T schoenleini	3
T violaceum and M sp †	1
T violaceum and T cerebriforme	1
M lanosum and T schoenleini	1
T niveum‡ and T cerebriforme	1
E inguinale and T purpureum§	1

*Included are 3 cases in which no cultural methods were employed

†The clinical features warrant this inclusion. Species was not mentioned

‡Reported as *Trichophyton niveum denticulatum*§Reported as *Epidermophyton rubrum* like fungus

"favus-trichophytosis" combinations would reduce the number of fungous associations observed on the scalp to seven. The most frequent was the joint occurrence of *Trichophyton violaceum* and *Trichophyton schoenleinii* (eight times). The combination of *T. crateriforme* and *T. schoenleinii* was reported three times. Each one of the following combinations is on record: *T. schoenleinii* and *Microsporum lanosum*, *T. violaceum* and *Trichophyton cerebriforme*, *Epidermophyton floccosum* and *Trichophyton purpureum*, *Trichophyton niveum* and *T. cerebriforme* and *T. violaceum* and *Microsporum* "sp" (species not reported).

Microspora were listed only twice, once in combination with *T. schoenleinii* and once with *T. violaceum*. The microsporum occurring in conjunction with *T. violaceum* was not identified, the other was *M. lanosum*.

This paper presents the history and critical evaluation of the first recorded case of a scalp infected with both *Microsporum audouinii* and *M. lanosum*.

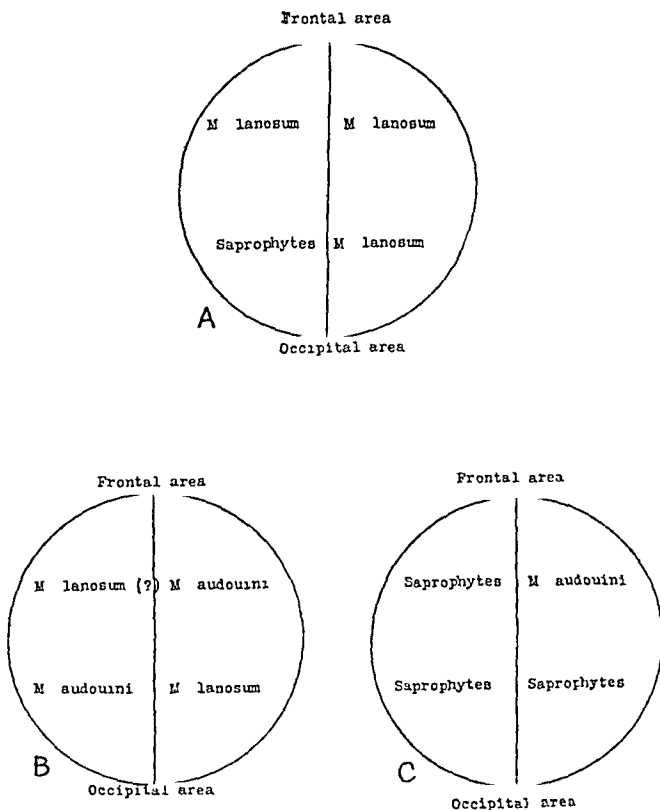
REPORT OF A CASE

On March 14, 1946, an 11 year old Negro girl was referred to the outpatient department of the Long Island College Hospital with the diagnosis of *tinea capitis*. *M. audouinii* had been identified as the causative fungus in January 1945. The patient had been treated unsuccessfully with various salves and tincture of iodine for fifteen months, both prior and subsequent to epilation with roentgen rays in January. Examination on admission to the clinic of the Long Island College Hospital showed small spots of "gray patch" ringworm scattered on the scalp. Signs of inflammation were absent. The gray patches disclosed groups of bright fluorescent hairs under filtered ultraviolet rays. Culture of fluorescent hairs yielded *M. audouinii*, confirming the observations of the previous investigator. This initial examination was followed by eleven months' treatment, during which the fungicidal agents employed failed to produce any substantial effect. These agents included ammoniated mercury ointment, compound ointment of benzoic acid, sulfur ointment, a compound containing iodine, thymol, camphor and oil of eucalyptus in olive oil, "desenex" ointment (contains 5 per cent undecylenic acid and 20 per cent zinc undecylenate in an ointment base), 5 per cent salicylanilide in "carbawax" (polyethylene glycol) and cetyltrimethylammonium pentachlorophenate, together with manual epilation. The patient attended the clinic at weekly intervals. On Feb. 20, 1947, the mycologic examination of fluorescent hairs of the scalp was repeated. The culture yielded *M. lanosum*. Repetition of the tests on March 4 and March 18 showed *M. audouinii* on the former and *M. lanosum* on the latter date.

Because of these apparently contradictory results of the laboratory studies, cultures were taken separately, on April 1, from the left and right frontoparietal areas and from the right and left occipital areas. The right and left frontoparietal as well as the right occipital area yielded *M. lanosum*. The culture of the left occipital area was overgrown with saprophytic fungi and bacteria, pathogenic dermatophytes were not obtained from that area (*A* of the figure). On April 15, cultural examination of the four areas was repeated. *M. lanosum* was identified in the right occipital area and *M. audouinii* in the left occipital and right frontoparietal region. The tube containing the inoculum from the left frontoparietal area was accidentally broken before microscopic examination of culture material could be

performed. The rate of growth and the color of the colony, however, were indicative of *M. lanosum* (*B* of the figure). On May 27, cultures from the aforementioned four areas of the scalp yielded *M. audouinii* only in the right frontoparietal region, the tubes from the other areas were overgrown by saprophytes (*C* of the figure).

It is noteworthy that the clinical character of the infection remained invariably and uniformly that of "gray patchy" ringworm, without signs of inflammation. During the period of repeated mycologic studies, the topical applications of therapeutic agents was continued, except on the days of and preceding the visits to the clinic. The patient had menstruated, at irregular intervals, since the beginning of



Diagrams showing cultural results in each area. *A*, results of cultures on April, 1, 1947; *B*, results on April 15; *C*, results on May 27.

1946. The blood cell count in March 1946 revealed a moderate degree of anemia, with 3,590,000 red blood cells and 10.5 Gm of hemoglobin. The white cell count was 5,950, with 50 per cent neutrophils, 44 per cent small lymphocytes and 6 per cent eosinophils. No abnormal red or white blood cells were seen. The cholesterol content of the blood was 210 mg per hundred cubic centimeters.

METHOD AND DIAGNOSTIC CRITERIA

The mycologic diagnosis was based on accepted technics and criteria. Infected hairs, identified by filtered ultraviolet rays, were placed on Sabouraud dextrose agar slants (Difco). Each slant was inoculated with

ten hairs. The tubes were kept at room temperature and observed for signs of fungous growth for at least three weeks, at intervals of from two to seven days. When a fungous colony had reached a diameter of about 2 cm. material from its center was taken for microscopic examination and subcultures were performed on three other dextrose agar slants. The latter were kept under macroscopic and microscopic observation for a period of at least six weeks.

M. lanosum developed quickly and grew relatively rapidly, it covered the entire surface of the agar slant in an average period of from seven to fourteen days. The aerial mycelium was relatively abundant. In younger colonies a yellow lemon-colored pigment appeared, particularly conspicuous when viewed with transmitted light. As the colony aged, its color changed from yellow to brownish red. At a still later stage of development, the surface, principally at the center of the colony, became powdery.

M. audouinii started to grow later, and its rate of development was slower than that of *M. lanosum*. It took from two to four weeks to cover the entire surface of the agar slant. The aerial mycelium was closely matted and relatively scanty. There was no yellow lemon-colored pigment present; instead, a brownish red pigment appeared relatively early on the under surface of the colony.

The color of the growth could be relied on as a differential diagnostic criterion only in the early stages of the cultures. With increasing age a diffuse brownish red pigment pervaded the colonies, which made the difference in pigmentation an unsafe diagnostic criterion.

Exact diagnosis of the nature of the colony was made by microscopic examination of culture mounts. The characteristic feature of *M. lanosum* was the large amount of macroconidia of the tapering fuseaux type, with four to seven compartments. These were seen on mounted slides as early as five days after transplantation and remained demonstrable as late as one hundred and forty-four days. Fuseaux of this type were practically absent in culture mounts of *M. audouinii*.

COMMENT

The facts of special interest in this case are as follows:

In a Negro girl, near sexual maturity, ringworm of the scalp developed which was extremely resistant to treatment for at least two and

one-half years. At an earlier stage of the infection *M. audouinii* was seen by two observers, with an interval of about one year between each examination. Eleven months after the initial examination at the clinic of the Long Island College Hospital (presumably more than two years after onset of the symptoms) a mycologic study revealed the presence of *M. lanosum* as well as *M. audouinii*. Thereafter both fungi were demonstrated repeatedly. Although both fungi were never grown together on the same agar slant, they were demonstrated simultaneously and consecutively at close proximity, e.g., on April 15, 1947 *M. lanosum* was isolated from two areas of the scalp and *M. audouinii* from two others. Furthermore, on April 15 and May 27, *M. audouinii* was identified in an area from which *M. lanosum* had been isolated on April 1.

A comparison of *A* and *C* of the figure suggests the possibility that the combined infection might have been localized in the right frontoparietal area. At this site *M. lanosum* and *M. audouinii* were identified alternately, while in the other three areas the serial tests revealed either the identical dermatophyte or a saprophyte.

The two different fungi could not be correlated with two different types of lesions of the scalp. Uniformly, there was lack of inflammatory response. As a matter of fact, at a later stage of the infection, only filtered ultraviolet rays disclosed the presence of affected hairs. This mild clinical course, characteristic of the majority of the anthropophilic infections, prevailed throughout the period of observation.

Although no conclusive evidence can be adduced, it is likely that the *M. audouinii* infection antedated the combined infection of the scalp. This statement is based on the facts that two observers saw only *M. audouinii* within one year and the clinical appearance was that commonly seen in *M. audouinii* infections. At some later date a superimposed infection with *M. lanosum* may have taken place. It is noteworthy that the character of the disease did not change and no inflammatory response occurred.

The question as to whether the close association of the two fungi was instrumental in this unusual resistance to all therapeutic agents used cannot be decided at this juncture. It appears to be linked up with another problem, namely, whether combined infections are in reality as rare as the sparse reports of the literature seem to indicate. Practically all cases of combined fungous infections reported came to light rather by

accident than by deliberate search. It seems possible that a systematic approach by repeated laboratory studies at intervals would uncover more cases. In this manner, light might be thrown on a possible causal relation between resistance to treatment and double infection.

SUMMARY

A case of tinea capitis is reported in which both *Microsporum audouinii* and *Microsporum lanosum* were present. The clinical appearance was at all times and in all sites that commonly seen in the anthropophilic type of the disease. There was no response to the therapeutic agents employed.

It is suggested that material for examination in cases of suspected or proved fungous infection of the scalp be taken from several diseased sites and that such examinations be repeated at relatively frequent intervals.

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TREATMENT OF EARLY SYPHILIS WITH PENICILLIN IN OIL AND WAX

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THE TREATMENT of syphilis with penicillin as an office procedure is highly desirable, since for social or financial reasons many patients wish to avoid hospitalization. The delayed absorption of penicillin in peanut oil and wax permits the use of this preparation on an ambulatory basis, and several reports have appeared in which this form of treatment has been shown to be satisfactory in the treatment of early syphilis¹

During the past year I have used penicillin in oil and wax alone in the treatment of 78 patients with primary and secondary syphilis. This report presents the results obtained and the untoward reactions that I observed in this group of patients.

MATERIAL AND PROCEDURE

From February 1946 to August, 78 patients with early syphilis were treated with penicillin in oil and wax. Three of these patients failed to return for follow-up observation and are not included in this report. Of the remaining 75 patients, there were 35 male and 40 female patients, 6 were white, and 69 were Negro. The diagnoses at the onset of treatment were primary syphilis in 14 patients, secondary syphilis in 44 patients and recurrent secondary syphilis in 17 patients.

The diagnosis of early syphilis was confirmed in 41 patients by the demonstration of *Treponema pallidum* in the lesions. In 31 cases the diagnosis was based on typical cutaneous lesions of secondary syphilis, associated with strongly positive serologic reactions. The remaining 3 patients showed no cutaneous lesions, but had other manifestations of early syphilis, such as decided generalized lymphadenopathy, iritis and a rising serologic titer.

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From the Clinic for Genitoinfectious Diseases, Grady Hospital, Department of Medicine, Emory University School of Medicine, and the Georgia Department of Public Health.

1 (a) Rommanky, M J, and Rein, C R. Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, *J A M A* 132:847 (Dec 7) 1946. (b) Thomas, E W, Landy, S, and Cooper, C. Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil, *J Ven Dis Inform* 28:19, 1947. (c) Koch, R A. Ambulatory Intensive Treatment of Syphilis with Calcium Penicillin in Oil and Wax, *Urol & Cutan Rev* 50:461, 1946.

Only 2 patients had negative reactions to serologic tests for syphilis, both of these had primary lesions with positive results on dark field examination. The patients in whom the disease was diagnosed as recurrent secondary syphilis were patients in whom evidence of secondary syphilis had developed following previous treatment with aqueous solution of penicillin or arsenic and bismuth compounds.

A quantitative Kahn test of the blood and a spinal fluid examination were performed for every patient before treatment was started. Cell counts of the spinal fluid were done in the Fuchs-Rosenthal chamber within an hour after the spinal fluid was taken. Total protein determinations in the spinal fluid were made by electrophotometric measurement of the turbidity produced by the addition of sodium sulfosalicylate to the spinal fluid. The electrophotometer had been standardized with serum, the total protein of which had been determined by the Kjeldahl method. Colloidal tests were done with mastic solution. The Kolmer complement fixation tests were done with serial dilutions of spinal fluid from 0.5 cc. to 0.0312 cc.

Four patients had positive Wassermann reactions of the spinal fluid, 2 of whom also had an increase in the spinal fluid cell count and protein. One of these 4 patients showed unilateral facial paralysis and evidence of meningitis due to syphilis.

Two ambulatory treatment schedules were employed, each consisting of a total dose of 9,600,000 units of penicillin in wax and oil. One group of 52 patients was given daily injections of 600,000 units for sixteen days. The second group, consisting of 23 patients, received an injection of 600,000 units twice a week for eight weeks. The schedule selected for each patient depended chiefly on the convenience of the patient and not on the severity or type of illness. All patients were instructed to return at monthly intervals for repeated serologic tests. Although no further treatment was advised following the completion of treatment with penicillin in oil and wax, 3 patients received a few additional injections with arsenic compound or penicillin from their private physicians for either pregnancy or a persistently positive serologic reaction. Seventeen patients were observed for six to nine months, 17 for ten to twelve months and 34 for thirteen to nineteen months. Seven patients had a relapse within six months after treatment and were given another form of treatment.

RESULTS

The table shows the results of the penicillin therapy in the 75 patients. Fifty-two of the patients (69.3 per cent) attained a negative reaction to the serologic test for syphilis, which was maintained throughout the period of observation. The length of time required to attain a negative reaction varied considerably. Although negative serologic reactions were attained in a few patients by the third month, four to seven months were usually necessary. Occasionally as long as twelve to fifteen months were required before the serologic reaction became negative.

Only 8 patients in this series continued to show a positive reaction to the serologic test for syphilis. The Kahn titer in each of these 8 patients was steadily decreasing, and, at the time of writing, the titer in all but 1 was less than 4 Kahn units. This patient continued to have a positive reaction, with 20 Kahn units after one year of treatment for recurrent secondary syphilis. Follow-up observation in these 8 cases must be

continued, however, to determine their ultimate serologic and clinical outcome

In 15 (20 per cent) of the 75 patients in this study treatment was considered to have failed, and these patients showed serologic or clinical evidence of an active infection following treatment with penicillin in oil and wax. In 9 of the 15 recurrent cutaneous lesions of early syphilis developed, while 5 others showed a rising serologic titer without lesions. In the remaining patient treatment was considered to have failed because no change had occurred in the spinal fluid cell count after four months of treatment with penicillin in oil and wax for recurrent secondary syphilis with meningitis due to syphilis.

In 4 (23.4 per cent) of the 17 patients in whom the disease had been diagnosed as recurrent syphilis prior to treatment, evidence of an active syphilitic process again developed following the penicillin therapy. This is somewhat higher than the number of patients with relapse (18.9 per cent) among the patients treated for the first time.

The relative efficacy of the two treatment schedules employed in this study is of interest. Failure of treatment occurred in 11 (21.1 per cent) among the 52 patients treated with daily injections, whereas failure occurred in 4 (17.1 per cent) among the 23 patients treated twice a week. While the number of patients in each of these groups is rather small and definite conclusions cannot be made, it appears, nevertheless, that the results obtained with injections of penicillin in oil and wax two times a week were at least as good as those obtained with daily injection.

At least 2 of the 15 patients in whom treatment was classified as having failed in this study appeared to have reinfections rather than relapsing infections. One of these patients was a Negro who had been treated for seronegative primary syphilis. Six months following treatment he returned with another seronegative primary lesion at a site different from that of the initial chancre. His wife had been treated in this clinic for secondary syphilis and had presented recurrent secondary manifestations several weeks prior to the time of the appearance of her husband's lesion. The second patient, a Negro, had attained a negative reaction to the serologic test for syphilis three months after treatment for secondary syphilis. He returned five months after treatment, however, with a primary lesion and a doubtful reaction to the serologic test. When first treated with penicillin in oil and wax, he had given the name of the only person whom he had contacted, who was referred to another clinic for treatment. It was not until the patient returned with another lesion that it was learned that the person whom he had contacted had never received treatment and had, in the meantime, married the patient. Two other patients with recurrent syphilis also presented what appeared clini-

cally to be reinfection rather than relapse, but this, of course, could not be proved ²

Examinations of spinal fluid were repeated in all cases of relapse and for the 4 patients who had had positive reactions of the spinal fluid before treatment. In none of the patients with initially negative reactions of the spinal fluid and subsequent clinical or serologic relapse did there develop a positive reaction of the spinal fluid. Three of the patients with initially positive reactions of the spinal fluid had a satisfactory serologic response, and the spinal fluid in these patients became normal. The remaining patient, as mentioned in a foregoing paragraph, showed no reduction in spinal fluid cell count four months following treatment with penicillin in oil and wax for recurrent secondary syphilis with meningitis due to syphilis.

REACTIONS

The reactions encountered with the penicillin therapy were generally minor and consisted chiefly of pain and tenderness at the site of injection. In a few patients local pain and tenderness became rather severe after the eighth to the tenth injection, and considerable encouragement was necessary before these patients consented to continue treatment.

Leukocyte counts and differential examinations of blood smears were done for 28 patients. Fourteen of these showed definite eosinophilia, the percentages of eosinophils ranging from 6 per cent to 35 per cent. In 5 patients urticaria developed, which responded promptly to treatment with diphenhydramine hydrochloride ("benadryl hydrochloride").

Herxheimer reactions were encountered in a few patients. Since all the patients in this study were ambulatory, only the severe reactions were noted and probably many of the milder ones were unobserved. In the majority of instances, the reactions consisted of fever, chilly sensations, headache and temporary exacerbation of symptoms.

Although the mucosal and cutaneous lesions usually disappeared rather rapidly with treatment with penicillin in oil and wax, I observed 2 patients in whom papular secondary lesions continued to develop during the first seven to ten daily injections of the penicillin mixture. Some of the older lesions in these patients showed signs of involution and healing, but fresh lesions continued to appear. Results of dark field examinations were negative for these 2 patients when examinations were repeated during the first week of treatment. The number of papules had increased to such an extent during the first week of treatment that change of treatment was contemplated. Histologic examination of the papules revealed

² Moore, J. E. The Changing Concept of Reinfection with Syphilis and Its Applicability as a Criterion of Cure, editorial, *Am J Syph, Gonorr & Ven Dis* 29:474, 1945.

an acute reaction in addition to the syphilitic process. The detailed histologic observations for these 2 patients will be reported elsewhere.³ Although papular secondary syphilides are known to heal slowly, I have never observed this phenomenon with arsenical therapy. I believe that these patients may have had an unusual form of Herxheimer reaction, manifested by a prolonged exacerbation of cutaneous lesions.

In 1 patient pulmonary emboli developed following the intramuscular injection of penicillin in oil and wax. This patient had a severe attack of coughing while still on the treatment table and complained of tasting the medication. Several days later fever and severe dyspnea developed, and the patient was hospitalized. Roentgenographic examination of the chest revealed multiple areas of pulmonary consolidation. The patient was extremely ill for several days, but eventually recovered with symptomatic therapy. This case has been reported in detail elsewhere.⁴ I have since observed 1 other patient not included in this series, who had a pulmonary embolus following treatment with penicillin in wax by injection.

COMMENT

The results obtained in this study indicate that penicillin in oil and wax is as effective in the treatment of early syphilis as aqueous penicillin. There were 11 (18.9 per cent) patients for whom treatment failed among 58 patients treated for primary and secondary syphilis and 4 (23.4 per cent) with relapse among the 17 patients with recurrent syphilis. Thomas, Landy and Cooper^{1b} obtained similar results in a large number of patients with early syphilis. These workers used doses of 4,800,000 units of penicillin in oil and wax in eight days. The number of patients with relapse or reinfection in their series after follow-up of at least six months was 13 per cent of 392 patients treated for primary and secondary syphilis and 37 per cent of 30 patients who had had previous treatment for syphilis. Although the dose of penicillin in oil and wax used by Thomas and his associates was half that given to the patients in this study, the results do not appear to be significantly different. This is not surprising, however, for studies of treatment with aqueous penicillin in early syphilis have shown that there is little difference in the results obtained when doses greater than 2,400,000 units are given. It seems probable that the amount of penicillin used in my patients was excessive and that smaller doses may be equally effective.

Injections of penicillin in oil and wax given twice a week appeared to be as effective as daily injections of the drug. This observation was of

3 Sheldon, W. H., and Heyman, A. To be published.

4 Bondy, P. K., Sheldon, W. H., and Weens, H. S. Pulmonary Embolism Caused by Penicillin-Oil-Beeswax. An Experimental Investigation with Report of a Near-Fatal Case, *Am J Med* 3:34, 1947.

interest, since little or no penicillin remains in the patient's blood thirty-six to forty-eight hours after the injection of 600,000 units of penicillin in oil and wax. Experiments with syphilis in rabbits, however, have suggested that constant maintenance of measurable levels of penicillin may not be necessary in treatment for syphilis.⁵ It would appear, therefore, that strict adherence to daily treatment with penicillin in oil and wax may not be necessary and that more convenient schedules of two or three injections a week may be successfully employed.

The number of untoward reactions encountered with treatment with penicillin in oil and wax is somewhat greater than with treatment with aqueous penicillin. The most troublesome reactions were local pain and urticaria. The latter responded well to the administration of diphenhydramine hydrochloride, and the simultaneous use of this drug with penicillin in oil and wax was successful in preventing recurrence of this reac-

Results of Treatment with Penicillin in Oil and Wax (9,600,000 Units)

	Total No. of Patients	Treatment Failure	Sero- negative Reaction	Sero- positive Reaction
Primary syphilis	14	3*	11	0
Secondary syphilis	44	8*	30	6
Recurrent syphilis	17	4	11	2
Total	75	15 (20%)	52 (69.3%)	8 (10.6%)

*At least 1 of these patients appeared to be reinfectd

tion. Treatment had to be discontinued in only 1 patient, and this was the patient with pulmonary emboli. This accident occurred despite the usual precautions observed in injecting insoluble material. Although similar episodes have not been experienced in other clinics in which large quantities of penicillin in oil and wax have been used,⁶ it is certainly a danger and care must always be employed in administering this drug.

The cost of the large amounts of penicillin in oil and wax required for the treatment of early syphilis is not excessive, considering the cost and inconvenience of hospitalization necessary with the use of aqueous solutions. Ambulatory schedules with penicillin in oil and wax, however, have one disadvantage, with respect to a large clinic group, and that is the occurrence of delinquency, particularly if treatment is prolonged to eight weeks or more. Several of my patients missed one or more

5 Eagle, H., Magnuson, H. J., and Fleischman, R. The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, *Bull. Johns Hopkins Hosp.* **79**: 168, 1946.

6 Thomas, Landy and Cooper.^{1b} Romansky, M. J. Personal communication to the author.

treatments, and it was only by constant case-holding efforts that I was able to obtain completion of treatment in all of the patients

SUMMARY AND CONCLUSIONS

A group of 78 patients with primary and secondary syphilis were treated on an ambulatory basis with 9,600,000 units of penicillin in oil and wax. Fifteen (20 per cent) of the patients followed up for six to nineteen months presented evidence that treatment had failed.

The commonest reactions to treatment with penicillin in oil and wax were local pain, urticaria and eosinophilia.

Penicillin in oil and wax appears to be as effective in the treatment of early syphilis as aqueous penicillin and provides a convenient method of treating this stage of the disease.

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KERATOSIS PILARIS RUBRA ATROPHICANS FACIEI

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REPORT OF A CASE

A WHITE girl, R. J., 16 years old, was first seen in July 1940. The condition of her skin had been present since early childhood and had not changed much. As shown in the genealogic chart, it was a hereditary condition and had resisted every type of treatment up to the time of examination. The photographs show the condition better than any description could. The profile view is identical with the picture in "Nouvelle pratique dermatologique"¹. There were two different conditions of the skin present. The maxillary regions of both cheeks showed pigmentation of different shades, forming a network of light and dark brown flecks. The whole region was affected, without a single spot of normal skin inside the border on both cheeks. Close observation revealed fine scarring intermingled with small areas of chronic dark red inflammation. There was no facial down visible in the entire affected area. The middle of the forehead showed a similar change of the skin, however, this was less pronounced. The scars were not so definite, and the follicular origin was more noticeable than on the cheeks. The affected area was of triangular shape, with the apex between the eyebrows and descending to the bridge of the nose. There were never any lesions present in the eyebrows.

There was a second feature of the disease, which has not been described in the few published cases of this disease. The areas of both cheeks adjoining the nose were covered with large pores. The location was symmetric. The openings were wide, as can be seen in the full face photograph. There was no inflammation or scarring visible. This condition had also been present since early childhood. On the extensor surface of the arms and legs, the skin showed the typical picture of lichen pilaris.

Genealogic Data The mother of the patient, 36 years old, presented the same condition as described except that it was not so well defined.

From Mount Sinai Hospital, Cleveland

¹ Darier, J., and others. *Nouvelle pratique dermatologique*, Paris, Masson & Cie, 1936, vol. 7, p. 89.

A younger sister, aged 13, had a normal skin. This girl resembled her father more than her mother. The youngest child, a sister who was 11 years old, had the same condition as R. J., however, it was even less pronounced than the mother's condition. According to the family history the disease was passed on by the great-grandfather and the grandfather

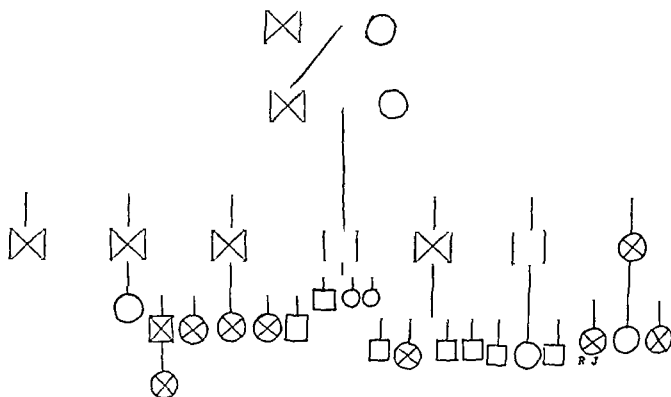


Fig. 1—Genealogic chart of the family of R. J., showing the incidence of *keratosis pilaris rubra atrophicans faciei*.



Fig. 2—Front and profile views of R. J., showing the extent of the disease on the face.

The grandfather had had 7 children, 6 boys and 1 girl, the mother of the patient. Two of R. J.'s uncles did not have the disease. Only 3 of the other men afflicted with the disease had families. An uncle, twelve years older than R. J.'s mother, had 5 children, of whom 4 had the same disease. The oldest one, a man, was married and had a small daughter, who had the disease. The other 3 children of this family who were af-

flicted were girls. Another married uncle who had the disease had 4 children, 3 boys and 1 girl. Only the girl had this disease. In a survey of the five generations, as can be seen from the chart, both sexes in about the same proportion had the disease. However, in the fourth generation, a predominance among the female members is apparent.

CLINICAL DESCRIPTION

In 1889 Brocq² presented the case of a 10 year old girl with a disease diagnosed as *keratose pileaire* or *xerodermie pileaire symmetrique de la face*. The patient had had, as an infant, a psoriasis-like eruption. The present disease had started when she was 3 or 4 years old and had developed slowly. When the patient was first seen, in 1888, there were two symmetric plaques on her forehead, above the eyebrows. Small elevations of the skin, which were pointed or slightly rounded at the top and more or less colored, were visible between the eyebrows and on the forehead outside the plaques. In the center of almost every one there was a lanugo hair. Groups of these papules and the inflammation from the two plaques extended over the eyebrows.

The dermatitis on the sides of the cheeks, however, did not have the same appearance. Here again were the small pointed elevations of the skin, one series adjacent to the next, forming two large symmetric lesions which occupied the entire side of the cheeks. There were fine vascular telangiectases. This new eruption was distinctly apparent near the ear. The lichenoid elevations were noticeable on the border of the plaque on the anterior part of the cheek. There were also some of these small elevations sprinkled over the margin of the jaw and the ear lobe.

When the patient's brother was 5 years old, he had the same disease in the area of the eyebrows and on the sides of the cheeks. Brocq saw 2 other cases of *lichen pileaire de la face* and described the development of the disease as follows:

(1) Beginning, in infancy, slow, gradual, and almost unnoticeable development.

(2) Distinctive localization. In the eyebrows, together with some thinning of the hair, and on the forehead over the eyebrows, on the sides of the cheeks and the adjacent parts of the neck, the region between the eyebrows, and the chin.

(3) Absolute symmetry.

(4) Thousands of tiny lichenoid, partly squamous eruptions in the center of which there are often lanugo hairs and which are entirely colorless and isolated. Later there is a tendency to form groups by multiplication of the original lesion which rarely increases in its size.

2 Brocq, L. *Lichen pileaire ou xerodermie pileaire symmetrique de la face*, Ann de dermat et syph 10 339, 1889. Notes pour servir a l'histoire de la *keratose pileaire*, ibid 1 25, 97 and 222, 1890. Quelques remarques sur les alopecies de la *keratose pileaire*, Monatsh f prakt Dermat 15 609, 1892. Alopecies, in La pratique dermatologique, Paris, Masson & Cie, 1901, vol 1, p 301.

(5) Finally a vascular component which is purely erythematous and appears where there are multiple lichenoid eruptions. This later becomes very marked and some slight swelling of the skin occurs. Telangiectasis develops very quickly on the side of the cheeks. This gives the affected parts a somewhat purplish tinge.

It is interesting to note that Brocq mentioned that Wilson,³ in his lectures on dermatology in 1878, described the disease and called it "folliculitis rubra." He gave the following description:

There is a distinct form of hyperaemic congestion or subacute inflammation of the follicles which is associated with the congenital malnutrition and feebleness of the skin. It is restricted to the follicles and its identity is easily determined by the presence of red puncta, more or less prominence of the aperture of the follicle, and a loaded state of its excretory duct, which is distended with epithelial exuviae. Its seat is also pathognomonic, the eyebrows, the maxillary region of the cheeks, and the back of the upper arms and, from its self-evident pathological nature, it has seemed to me to be well expressed by the term "folliculitis rubra."

Folliculitis rubra is met with in children and young persons, more particularly in those of the female sex and occasionally in the adult. It is at once recognized by a suffused redness of the lower part of the forehead, the eyebrows, and side of the cheeks, and, if from these parts, we proceed to the back of the upper arms, we shall very probably find them bright red in color and studded with minute papulae closely patched together looking like obliterated follicles and communicating a sense of roughness to the hand when passed over them. A closer examination detects the depth in the skin to which the hyperaemia extends, and the minute plugs of loosened epithelium afford evidence that the whole extent of the follicle is involved. Moreover, a still more important sign presents itself, the hairs growing from the follicles have, many of them, fallen out and in the course of time the eyebrows will become entirely denuded, the outer half first and then throughout the rest of their length.

Cause. The cause of this state of the skin is, essentially, defect of nutrition power operating in a congenital and sometimes hereditary weak skin. I was much struck with the presence of this affection in a family of three or four young ladies, the daughters of a gentleman whom I knew to be the subject of ichthyosis, with which defect of the skin folliculitis rubra is closely aligned. Folliculitis rubra is very little amenable to treatment and often resists our best endeavors to promote its cure.

The relationship between keratosis pilaris rubra atrophicans faciei and ulerythema ophryogenes is sometimes mentioned. Some authors⁴ described cases in which apparently both of these diseases were combined in 1 patient. It seems necessary to refer to the original paper of Taenzer,⁵ in which the first description of ulerythema ophryogenes was published and which referred to it as "a skin disease undescribed up to the present

3 Wilson, E. Lectures on Dermatology, London, J & A Churchill, 1878, pp 217-220

4 (a) Siemens, H. Dermat Wehnschr 112 281, 1941 (b) Moncorps, C, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927-1932, vol 8, pt 2, pp 109-110

5 Taenzer, P. Ueber das Ulerythema ophryogenes, eine noch nicht beschriebene Hautkrankheit, Monatsh f prakt Dermat 7 197, 1889

[1889]" Taenzer reported 6 cases, 3 of them in the same family, and accentuated the characteristic features of the disease as follows

The beginning in earliest youth with reddening of the skin of the eyebrows which later spreads over the neighboring parts of the skin especially the face and the scalp but only very rarely over the upper arms The picture is one of non-purulent folliculitis which ends in atrophy of the skin

The cases described were of a 40 year old mother, her 10 year old daughter and her 1 year old son, a 20 year old girl and her 8 year old brother, a 31 year old man and an 11 year old boy In all these cases, the disease started in the eyebrows, and Taenzer proposed the name ophryogenes (superciliare) to make it clear that this is a special disease

COMMENT

Brocq presented his first case of this disease in February 1889, at a meeting at the Hôpital St Louis One year later, he published a paper with remarks about the history of "keratosis pilaris" He supplemented this with a paper which he read at the second International Congress of Dermatology in Vienna in 1892 There have been few cases published since that time outside France

Halter⁶ described a case in a 42 year old man, with small lesions and slight atrophic changes in the eyebrows, cheeks and skull The patient described by Gaté, Cuilleret and Boyer⁷ was an 8 year old girl with acne decalvans, keratosis pilaris atrophicans et onychogryphosis of the toes Salin presented a case in which the diagnosis was keratosis pilaris rubra atrophicans faciei plus granulosis rubra nasi A family with the same disease was described by Covisa, Bejarano and Gay⁸ Two girls, 15 and 16 years old, respectively, were presented by Siemens, with a disease diagnosed as lichen pilaris and ulerythema ophryogenes Klumpp⁹ presented a case in which the diagnosis was "keratosis pilaris", Jack Wolf remarked that this clinical picture was described under the name "keratosis pilaris rubra atrophicans" by Brocq

Anderson¹⁰ presented a 3½ year old white boy with the same disease, with the remark that 2 other young children of the same family had a similar eruption

6 Halter, K Keratosis pilaris rubra trophicans, Urticaria, Zentralbl f Haut- u Geschlechtskr 57 5, 1937

7 Gaté, J Cuilleret, P, and Boyer, C E Acne decalvante Keratose pileaire atrophiante et onychogryphose des orteils, Bull Soc franç de dermat et syph 38 1033, 1931

8 Covisa, J S, Bejarano, J, and Gay, P J Hereditary Keratosis, Pilaris, Rubra Atrophicans of the Face, Actas dermosif 19 171 and 254, 1927

9 Klumpp, M M Keratosis Pilaris, Arch Dermat & Syph 46 904 (Dec) 1942

10 Anderson, N P Keratosis Pilaris of the Face, Arch Dermat & Syph 49 81 (Jan) 1944

Returning to the description given by Wilson and later by Brocq and the description given by Taenzer and Unna regarding ulerythema ophryogenes, it seems that these are two different conditions, each of which has a specific primary location and a typical course. However, there are combinations of the two which may occur in the same person, but one or the other of the diseases will dominate.

It should be kept in mind that ulerythema ophryogenes always starts in the eyebrows, apparently from an infection of the hair follicles, which progresses slowly and forms typical folliculitis with pus.

Keratosis pilaris rubra atrophicans faciei starts in the preauricular region of the cheeks and forehead, with slow primary infiltration of the hair follicle which never shows formation of abscesses (acute folliculitis). The inflammation progresses slowly during the years, invades the normal skin and forms scars. Since the development proceeds slowly, the varying degrees of atrophy produce a netlike appearance. As a consequence of the chronic inflammation, all hairs disappear in the diseased region. The disease never reaches the skin on the cheeks adjacent to the nose.

TREATMENT

Vitamin A capsules, 100,000 to 150,000 units a day, and non pills were administered internally. External treatment consisted of the administration of ultraviolet rays, daily baths in water to which sodium bicarbonate had been added and the use, after drying, of an ointment made of cod liver oil, salicylic acid and tar oil in a base of wool fat and petrolatum. There was temporary improvement, however as soon as the treatment was stopped the cutaneous condition returned to its former state. As for the preauricular regions, they did not become worse during the four years of observation, therefore, their condition seemed to be always the same.

SUMMARY AND CONCLUSIONS

A family with typical keratosis pilaris rubra atrophicans faciei is presented and the condition of the oldest child is described in detail. After reviewing the literature, it seems clear that there exist two cutaneous conditions, both of which may be hereditary. However, each is an entity with distinctive features. Both start in early youth, one at the temples and the other in the eyebrows. All of the patients also had keratosis pilaris on the typical locations of the body. There may be combinations of both; however, keratosis which starts in the eyebrows in early youth should always be designated ulerythema ophryogenes whereas keratosis pilaris with reddening of the skin and later scarification which starts outside the temples in front of the ears should be called keratosis pilaris rubra atrophicans faciei. The cause of both these diseases is unknown as yet and no effective treatment has been published.

AMINOPHYLLINE AS AN ANTIPRURITIC AGENT

III Comparison with Certain Other Theophylline Salts

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THE ANTIPRURITIC action of the parenteral administration of aminophylline (theophylline ethylenediamine) has been described in previous discussions¹ This communication is concerned with the comparison of this agent with certain other salts of theophylline Briefly, it has been demonstrated that many vasodilators, including xanthine derivatives and others, have similar effects on itching This group includes various theophylline salts, procaine hydrochloride, papaverine hydrochloride, nicotinic acid and calcium Lundy² injected procaine hydrochloride intravenously to relieve the itching of jaundice State and Wangenstein,³ using this agent in the treatment of delayed serum sickness, demonstrated that procaine hydrochloride given intravenously acts as a vasodilator Wirth⁴ pointed out that papaverine hydrochloride, which is also a vasodilator, has antipruritic properties Service⁵ observed nicotinic acid injected intravenously to be of benefit in urticaria and certain related conditions due to penicillin Calcium, which also has vasodilating properties, is often used as an antipruritic agent

Obviously vasodilation does not relieve itching Mechanical vasodilation does not stop itching Scratching and heat may aggravate the symptoms Vasodilators that act locally, such as counterirritants, also increase the severity of pruritus Drugs that produce vasodilatation on local administration, such as histamine, may also cause itching Cutaneous entities associated with dilatation of the involved blood vessels, as exem-

1 Epstein, E Theophylline Ethylenediamine as an Antipruritic Agent Preliminary Report, Arch Dermat & Syph **53** 281 (March) 1946, Aminophylline as an Antipruritic Agent II Intramuscular Injection, ibid **56** 373 (Sept) 1947

2 Lundy, J S Clinical Anesthesia, Philadelphia, W B Saunders Company, 1942, pp 392-393

3 State, D, and Wangenstein, O H Procaine Intravenously in Treatment of Delayed Serum Sickness, J A M A **130** 990 (April 13) 1946

4 Wirth, L Antipruritic Qualities of Papaverine Hydrochloride, J Invest Dermat **8** 63 (Feb) 1947

5 Service, W C Use of Nicotinic Acid in Treatment of Urticaria Due to Penicillin, Ann Allergy **4** 397 (Sept-Oct) 1946

plified by urticaria, are often characterized by pruritus. Therefore, it seems likely that mere enlargement of the blood vessels does not relieve itching.

According to the consensus, the end organs and nerve fibers conveying impulses of itching are the same ones that carry pain sensations.⁶ Pruritus is considered to be a subpain sensation. However, the evidence presented by this work with vasodilators suggests that the "itching center," if such a center is ever demonstrated, may be more closely related to the vasodilator center than to the pain centers in the brain.

COMPARISON OF THEOPHYLLINE SALTS

Itching is a subjective symptom that defies accurate measurement. Therefore, clinical impressions must be employed in evaluating results of treatment. Such measurements are notoriously inaccurate, because of personal feelings on the part of both the patient and the physician. However, the following impressions are based on the observations made by the presenting investigator in this group of patients.

Aminophylline—The previous communications were concerned exclusively with this agent.⁷ The results obtained in the alleviation of pruritus were considered to be promising but evanescent. The dangers of treatment with this drug, both disconcerting immediate reactions and possible fatalities, were reviewed. The more prolonged, but less dependable, benefits of intramuscular injection were also presented. The severe local reactions accompanying the latter route were stressed. Further studies with this agent have confirmed previously reported observations. However, the results obtained in 30 previously unreported cases of various pruritic dermatoses treated with intravenous injection of aminophylline are presented.

A dose of 0.5 Gm., administered in 20 cc. of diluent, was utilized in this series. Fifteen patients suffered with contact dermatitis, the disease in 11 being due to poison oak, in 2 to local medication and in 1 to geraniums, in 1 the cause was undetermined. There were 17 women and 13 men. Twenty-eight of the patients were white, the other 2 being Negro. The ages ranged from 15 to 64 years. Nearly 70 per cent of the patients were between 20 and 39 years of age.

Immediate complete relief was obtained in 24 patients (80 per cent). In these 24 patients the itching was stopped for an average of ten and eight-tenths hours. However, in some instances the freedom from itching

6 Sulzberger, M. B. Pruritus and Its Treatment, *M. Clin. North America* 19: 971 (Nov.) 1935.

7 The aminophylline used in this study was furnished by the Endo Products, Inc., Richmond Hill, N. Y.

lasted less than a half-hour. In 58.5 per cent of the cases, the relief lasted more than eight hours. The duration of relief varied in the same patient from injection to injection. The 30 patients received an average of two and seventh-tenths injections each. The maximum number of injections given to any patient was ten. It should be stated that the severity of immediate reactions limited the number of injections that any patient would take. The immediate symptoms included prickling sensations, syncope, dyspnea, nausea, vomiting (in 1 case) and tachycardia. In some patients, these symptoms persisted for hours.

Attempts were made to minimize these disconcerting reactions by increasing the dilution of the theophylline salt. Four patients were given 0.5 Gm. of aminophylline in 1,000 cc. of 10 per cent dextrose, with elimination of the immediate symptoms but without antipruritic effect. Six patients were given the same dose of aminophylline in 50 cc. of 10

Comparison of Results Obtained with Aminophylline, Theophylline Monoethanolamine and Theophylline Methylglucamine

	Aminophylline	Theophylline Monoethanolamine	Theophylline Methylglucamine
Number of patients	30	8	9
Number immediately and completely relieved	24 (80%)	6 (75%)	4 (44.5%)
Average complete relief	10.8 hr	7.3 hr	5.7 hr
Number of injections received by each patient	2.7	2.5	10.2

per cent dextrose, without significant changes in the rate and severity of the reactions. On the other hand, the therapeutic effect was lessened. Only 2 patients (33.3 per cent) experienced immediate cessation of itching. Furthermore, in these 2 patients, the relief lasted for an average of only four hours. One patient suffered a severer reaction with this dilution than with the same dose given in 20 cc. of diluent. On the whole, any decrease in reactivity could be attributed to the slower injection resulting from the increased volume of fluid administered.

Theophylline Monoethanolamine This agent⁸ was tested in 8 cases. The dosage was 0.5 Gm. administered intravenously in 20 cc. of diluent. The reactions and therapeutic results were similar to those obtained with aminophylline. Immediate relief was noted in 6 instances (75 per cent). The freedom from pruritus averaged seven and three-tenths hours in these patients. An average of two and five-tenths injections was given to this group.

⁸ The theophylline monoethanolamine used in this study was furnished by Eli Lilly and Company, Indianapolis.

From this it can be seen that this agent has antipruritic properties. Although this series is too small to be significant, the impression was gained that this drug is slightly less effective than aminophylline.

Theophylline Methylglucamine—Nine patients with various itching dermatoses were treated by the intravenous injection of this agent⁹ in doses of 0.732 Gm. in 20 cc. of diluent. These patients received an average of ten and two-tenths injections, attesting to this drug's lesser reactivity in comparison with the two previously discussed theophylline compounds. Immediate complete relief was obtained in only 4 cases (44.5 per cent), signifying the definite, but less frequent, therapeutic results. In the 4 patients who obtained relief, the effect lasted an average of five and seven-tenths hours.

Comparison—In the table, comparison of the aforementioned agents is made. It demonstrates that aminophylline is probably the most effective agent of this group. Theophylline methylglucamine produces the fewest reactions. All three agents have definite antipruritic properties.

COMPARISON OF DERMATOSES

Of the 30 patients treated with aminophylline, 15 presented contact dermatitis. In 10 of these patients (66.6 per cent), the relief lasted more than eight hours. In 3 (20 per cent), immediate complete relief was obtained, but the freedom from itching lasted less than eight hours. In the other 2 patients (13.4 per cent), no results were obtained.

Two patients with fairly generalized atopic eczema were treated. Both experienced immediate relief. In 1, the relief lasted more than eight hours. Five patients with localized eczema, as on the hands, were treated with intravenous injection of aminophylline. All 5 were immediately relieved of the itching. However, this lasted for more than eight hours in only 2 instances.

Two patients with scabies were treated with little success. Similar results were obtained in 2 patients with lichen planus. The results of treatment with this agent in 1 case each of urticaria and of pruritus ani were also disappointing. One patient with toxic dermatitis and 1 with flea bites reacted more favorably to this treatment.

This series is too small to be significant, but in a general way supports the impression that theophylline salts are more valuable in acute than in chronic pruritic conditions.

COMMENT

Treatment with neither aminophylline nor any of the other vasodilators mentioned in this communication can be considered to be the ulti-

9 The theophylline methylglucamine used in this study was furnished by Abbott Laboratories, North Chicago, Ill.

mate antipruritic technic. It is felt that these drugs represent substantial improvement over the other local, oral or parenterally administered remedies for itching. However, there are many related drugs to be studied in the hope of locating an ideal treatment for pruritus.

These agents apparently aid healing by disrupting the vicious cycle of itching leading to scratching, with more itching followed by further trauma. In a previous paper,^{1a} it was noted that healing occurred more quickly once the psychic and physical trauma of scratching was eliminated. This is of value in acute dermatoses, such as contact dermatitis. However, in chronic pruritic conditions, the relief of itching is only temporary, and the return of the pruritus and the resulting trauma reduce the patient to his pretreatment status. It is possible that, if this drug were given every four hours, even chronic eczematoid reactions would heal in a short period of time. However, the necessity for careful intravenous injection makes this impossible in private practice.

The value of the agents tested so far is limited by a combination of factors, including the necessity for intravenous administration, the annoying and possibly serious reactions and the evanescence of results. On the other hand, this approach offers great promise. The action is suggestive of that of morphine on pain. The desired effect is usually, but not always, obtained, it lasts about ten hours and is of symptomatic value.

Therefore, this communication should be considered as suggesting an approach to the problem of pruritus, but not the final solution.

SUMMARY

Evidence is presented demonstrating that the intravenous injection of certain vasodilators (theophylline salts, procaine hydrochloride, papaverine hydrochloride and others) may result in immediate complete relief of itching.

Aminophylline (theophylline ethylenediamine) seemed to be more effective than either of the other two theophylline salts studied.

Immediate complete relief of itching occurred in 80 per cent of the 30 patients treated with aminophylline, and this freedom persisted for an average of ten and eight-tenths hours.

These agents are more valuable in acute than in chronic pruritic dermatoses.

FAMILIAL URTICARIA DUE TO COLD

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THE APPEARANCE of urticarial wheals following exposure to cold is relatively common. Cooke¹ mentioned the case of Pepys, who suffered an attack of urticaria while walking in the park on a cold day in February 1663. Bourdon² in 1866 described urticaria and syncope due to cold, and in the same year Behier² described his own urticaria following exposure to cold. In an exhaustive study in 1936, Horton, Brown and Roth³ were able to find 76 cases in the literature in which hypersensitivity to cold was described.

Jadassohn and Schaaf⁴ reported the cases of a brother and a sister in whom wheals developed following exposure to cold. These urticarial lesions were chiefly confined to the hands and face. Kobacker and Parkhurst⁵ reported 3 sisters, in 1934, who had measles simultaneously. Shortly after their recovery it was noticed that these children would experience localized urticarial wheals following contact with a cold object. This sensitivity subsided and had completely disappeared at the end of one year.

From the Dermatological Section, Oliver General Hospital, Augusta, Ga.

1 Cooke, R A. *Allergy in Theory and Practice*, ed 1, Philadelphia, W B Saunders Company, 1947.

2 Cited by Horton, Brown and Roth³.

3 Horton, B T, Brown, G E, and Roth, G M. Hypersensitivity to Cold, with Local and Systemic Manifestations of Histamine-Like Character. Its Amenability to Treatment, *J A M A* 107 1263-1269 (Oct 17) 1936.

4 Jadassohn, W, and Schaaf, E. Kälteurtikaria bei zwei Geschwistern, *Dermat Wehnschr* 86 565-566 (April 28) 1928.

5 Kobacker, J L, and Parkhurst, H J. Cold Urticaria Following Measles in Three Sisters, *J A M A* 105 662 (Aug 31) 1935.

No case had been reported in which cold urticaria was due to a familial trait until 1940 Kile and Rusk⁶ gave a report of a patient in whom typical urticaria developed after exposure to cold This was accompanied with fever and joint pains In their case the family history revealed that 23 out of a total of 47 known relatives had this same allergy to cold This familial trait had been present for at least five generations

Urbach, Heiman and Gottlieb⁷ gave the history of a 22 year old man who had attacks of urticaria, fever and visible swelling of the joints after exposure to cold air This phenomenon had begun at birth, and 16 others out of 24 known members of his family had been similarly affected

We add a third case in which there was an extensive family history, the patient was seen at a United States Army hospital

REPORT OF A CASE

A 19 year old white soldier was admitted to Oliver General Hospital on Nov 19, 1946, with a chief complaint of urticaria and joint pains following exposure to cold This soldier was a native of South Carolina and had never been out of the "deep" South prior to his Army service

History—When the patient was 3 weeks old, it was noticed that his skin turned blue on exposure to cold and a few hours later the affected areas became erythematous In childhood, wheals resembling urticaria developed on the erythematous eruption Pruritus had never occurred with this wheal formation, although a mild burning sensation was sometimes present This cyanosis, followed by the urticarial rash, was accompanied with dull joint pains, the severity depending on the extent of the cutaneous reaction Despite the warm climate in which he lived he noted that he was hindered in his school work by the presence of this affliction, which was so incapacitating that it necessitated the loss of one to two days a week during the cold months of the year During the attacks of urticaria and arthralgia the patient suffered from chills and a slight elevation of temperature, and as he grew older the attacks became worse

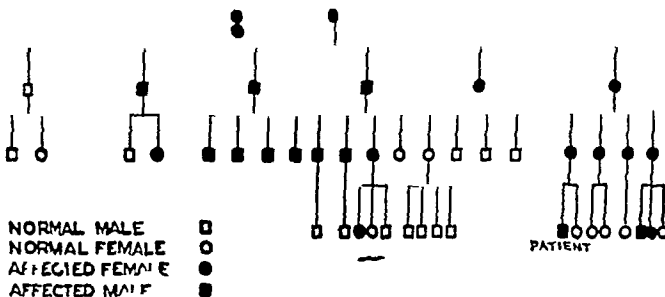
Induction into the Army took place on January 5, at Keesler Field, Miss While undergoing basic training on the warm Gulf coast, this soldier required hospitalization for ten days because of this idiosyncrasy to cold On being transferred to Scott Field, Ill he was hospitalized for an additional seventeen days During the summer of 1946, this patient was symptom free and later was sent overseas, arriving in Japan on October 1 While driving a truck in cold weather he experienced joint pains, accompanied with chills, and fever and cyanosis of his upper and lower extremities Symptomatic treatment brought about immediate relief Several nights later he was again exposed to cold and wind, became ill and was hospitalized Arthralgia was the chief complaint on admission, and a temperature of 101 F was noted Wheals, 1 to 2 cm in diameter, appeared on an erythematous base, involving the hands, forearms, feet and legs Pruritus was

6 Kile, R L, and Rusk, H A Case of Cold Urticaria with Unusual Family History, J A M A 114 1067-1068 (March 23) 1940

7 Urbach, E, Heiman, M F, and Gottlieb, P M Cold Allergy and Cold Pathergy, Arch Dermat & Syph 43 366-374 (Feb) 1941

absent, but during regression of the lesions stinging and burning was noticed. It was then decided that this patient was manifestly unfit for service, he was therefore returned to the United States. In the past this man had suffered from only those diseases common to childhood. He was told by his physician that he had "rheumatism," because of pain and swelling of the joints, fingers, wrists, elbows and ankles after exposure to cold.

Family History—There is no family history of cancer, tuberculosis or disease of the heart, lungs or kidneys. The chart demonstrates the incidence of this syndrome for four generations, with 24 persons affected. The patient's mother was a semi-invalid because of this condition. The same type of eruption with varying degrees of joint involvement and elevation of temperature occurred in all those who were affected. It was notable that no child was afflicted with this condition whose parent did not have it. It invariably began in early childhood and persisted throughout life. Pruritus was lacking in all those affected, though varying degrees of stinging and burning were present. No member of this family had lived in the northern part of the United States, where the intense cold might cause a severer reaction. Interestingly enough no member of this family suffered from other forms of allergy.



Genealogic chart showing the familial incidence of urticaria due to cold in the case reported.

Laboratory Data—Results of routine urinalyses and blood cell counts were always within normal limits. The sedimentation rate was 19 mm. Reactions to serologic tests for syphilis were negative. Prothrombin time, clotting time and bleeding time were determined, and all were normal. His basal metabolic rate was determined and was found to be +4 per cent. Roentgenologic studies of the chest and skull revealed no abnormalities.

Physical Examination—The patient was a well developed and well nourished white man, 19 years of age. His height was 69 inches (about 175 cm), and he weighed 180 pounds (about 82 Kg). The epidermis appeared normal when first examined, but after exposure to cold the thighs and ankles were somewhat cyanotic, later becoming erythematous. Numerous wheals, from 1 to 2 cm in diameter, appeared, with surrounding areas of blanching. These sometimes appeared on the trunk and upper extremities, but the sites of predilection were the inner surfaces of the thighs and the popliteal fossae. A few lesions of acne vulgaris were present on the face and shoulders, and mild tinea cruris was observed. The chest was clear to auscultation and percussion, and the heart was normal. The blood pressure was 120 systolic and 96 diastolic. Neurologic examination disclosed no abnormalities.

Course in Hospital—It was observed that this patient was most likely to experience an urticarial eruption following exposure to cold wind. The patient slept on the porch of his ward on several occasions, and the lesions would invariably appear. After full development and after the patient was placed in a warm room, the lesions slowly regressed and were gone in four to six hours. It was observed that a slight elevation of temperature, of 0.5 to 1 degree, accompanied this eruption, and mild arthralgia was his only complaint. He was given 50 mg of diphenhydramine hydrochloride ("benadryl hydrochloride") four times daily, with no apparent relief of the arthralgia or the urticaria. The dose was then increased to 100 mg of diphenhydramine, four times daily, and with this increased dosage a slight improvement in the condition was noted. The only side effect of this drug was moderate sleepiness. The patient at no time complained of pruritus, and no attack observed by us was sufficiently severe to warrant his confinement to bed. It was felt that this patient was unable to perform military duty, and he was separated from the service.

COMMENT

There are many points of similarity in our case and the cases of Kile and Urbach. In all the families the condition appeared shortly after birth in those affected. The attack was brought on in every case by cold, wind or extreme changes in temperature. The same syndrome was present in all three groups: urticarial wheals, lack of pruritus, presence of a burning sensation, pain and swelling of joints, chills and mild fever. In the studies, slightly over 50 per cent of the members of each family were affected. The ingestion of cold liquids had no discernible effect on oral mucous membranes.

Cockayne⁸ stated that in any allergic disease the number of affected male members of a family exceeds that of affected female members. It was noted by Kile that this was not true in his family study, and we noted that in both Urbach's and our cases the number of female members was greater.

SUMMARY

A case of familial urticaria due to cold in a 19 year old soldier is presented. There was an incidence of the identical syndrome in 24 out of 45 members of his family for four generations. Analogous studies have been made by Kile and Rusk⁶ (1940) and by Urbach, Herman and Gottlieb⁷ (1941). So far as we know, this is the third such case to be reported in the literature.

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8 Cockayne, E. A. *Inherited Abnormalities of the Skin and Its Appendages*, ed 1, London, Oxford University Press, 1933, p 364.

SALICYLANILIDE THERAPY IN TINEA CAPITIS

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AT PRESENT most dermatologists consider roentgen epilation the most efficient form of treatment for tinea capitis, particularly for the type caused by *Microsporon audouinii*. In the last few years this fungus has been the predominant causative agent of the prevailing tinea infections of the scalp of children in the eastern and central parts of the country. On the basis of my experience with about 1,000 patients treated with roentgen epilation, I definitely support this view. In the hands of the skilled operator roentgen epilation is safe and effective. To many patients and their parents, however, any therapeutic measure that produces baldness for several months is still rather drastic and objectionable. Then, too, in many communities where the disease is prevalent this form of treatment is not available because of the lack of proper equipment and trained personnel. It is obvious, therefore, that there is still ample room in the armamentarium of dermatologists for simpler, and yet effective, agents for the eradication of this disease.

In the light of these facts the clinician who has been dealing with the problem of tinea capitis in the last few years has been faced with a twofold task. First it was imperative that he institute promptly the best known curative and prophylactic measures in order to reduce the incidence of the disease and to return the children who had contracted the disease to their proper place in the community as quickly as possible. Second, the conscientious clinician was impelled at the same time to maintain a vigilant quest for simpler, and yet effective, curative agents. The first objective was reached mainly by the administration of epilating doses of roentgen rays to as many children as time and other factors permitted. In the search for other curative medicaments, an opportunity was afforded in the work with children whose parents or guardians refused treatment with roentgen rays, and desired other remedies. Another group was deliberately given a fair trial with one or more different medicaments in the clinic at Northwestern University before roentgen rays were administered. A third group of children afflicted with the disease

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had been treated with different topical applications before they were admitted to the clinic. In these circumstances one was able to observe the relative effectiveness of the different therapeutic agents used. The array of the various medicaments employed include well known substances in various strength and combinations, such as sulfur, salicylic acid, ammoniated mercury, mercury bichloride, tincture of iodine, iodine ointment, mercurochrome (5 per cent and 2 per cent solutions), benzoic acid, ointment of benzoic and salicylic acid, and the newer preparations, such as undecylenic acid, 5 per cent and 10 per cent ointment alone or in combination with zinc undecylenate, solution and ointment containing sodium propionate and propionic acid, a solution containing 1 per cent chlorazodin, solutions of dimethyl-benzyl-ammonium chloride, from 0.1 per cent to 3 per cent, and an ointment containing an antibiotic extracted from garlic. After months of trial with these remedies, only relatively few patients were really cured. The disease in many children showed favorable response at first, but, after reaching a certain point, remained utterly refractory to further treatment. Most of these patients were finally cured with roentgen epilation. Parents who refused treatment with roentgen rays struggled on with the topical applications for months and years, until either they changed their minds or time became a factor in the course of the disease.

The results obtained with the use of diethylstilbestrol, given daily in 0.5 mg oral doses to 60 boys with tinea capitis, were disappointing. Results from the first few weeks of this treatment were encouraging, but after four to six weeks treatment with the drug had to be stopped because the breasts of the boys became swollen and tender. When the breasts returned to a normal state, resumption of treatment with the same drug failed to bring further improvement in the scalp. Out of a group of 50 boys treated with androgenic substances orally and parenterally, only 3 were cured. This group also showed improvement in the early part of the course, and then the disease remained stubbornly resistant to further male hormone therapy. A detailed report of the study made with diethylstilbestrol and androgenic substances in tinea capitis will be available in a separate communication.

In November 1945, Schwartz,¹ of the Section of Dermatoses, United States Public Health Service, reported the favorable results which he and his co-workers had obtained in the tinea capitis epidemic in Hagerstown, Md., with the use of an ointment containing salicylanilide 5 per cent in "carbowax 1500" (a mixture of polyethylene glycols having an average molecular weight of about 500). In September 1946, a more detailed report of this work was published.² From December to July 1946,

1 Schwartz, L. Personal communication to the author.

2 Schwartz, L., and others. Control of Ringworm of the Scalp Among School Children, *J A M A* 132: 58-61 (Sept. 14) 1946.

this ointment was prepared in the clinic pharmacy and was given to the patients. From July to April 1947, an ointment containing the same ingredients and prepared in a local pharmaceutical laboratory was employed. This report deals with the results obtained in the treatment of 150 white patients with tinea capitis of the audouini type with the aforementioned ointment from December 1945 to April 1947, a period of approximately sixteen months.

CRITERIA FOR DIAGNOSIS AND CURE

A diagnosis of tinea capitis was made on the basis of the (1) history and clinical examination of the scalp and description of the lesion, (2) inspection of the scalp under the Wood light, (3) microscopic examination of the hairs mounted in 10 per cent sodium hydroxide or chloral lactophenol, (4) inoculation of Sabouraud's maltose agar slants with suspected hairs and (5) identification of the organism cultured.

A patient was discharged as cured when (1) after stopping all medication, three successive examinations under the Wood light, at least two weeks apart, failed to show the characteristic green fluorescence and (2) three separate inoculations of hairs on culture slants at least two weeks apart failed to show any growth characteristic of *M. audouini*.

The duration of treatment includes the six week period spent in observing the patients and cultures with the object of determining whether cure was effected.

METHOD OF TREATMENT

Each patient or parent was instructed as follows:

- 1 The hairs of the entire scalp must be clipped short to $\frac{1}{8}$ inch (about 0.32 cm) every ten days.
- 2 The ointment must be applied to the entire scalp once daily and to affected areas twice daily for three days.
- 3 The scalp must be washed on the fourth day and no ointment applied on that day. The three day treatment is resumed on the next day.
- 4 Tightly fitting caps made of boilable materials must be worn at all times. Fresh caps are supplied daily, and the old caps may be washed and boiled for five minutes every day with a solution of cresol added to the water.
- 5 The patient must present himself for examination at the clinic at least once every two weeks, and the scalp must be free from ointment at that time.

The progress of the disease was watched by biweekly clinical examinations and inspection of the scalp under the Wood light. Microscopic studies and cultures of the hairs were made during this period as conditions warranted them.

RESULTS OF TREATMENT AND COMMENT

Out of 150 white patients treated in the period of sixteen months, 124 were boys and 26 were girls. Of these, 105, or 70 per cent, were dis-

charged as cured, in this group there were 87 boys and 18 girls. The shortest period required to effect a cure was three months and the longest fourteen months, thus giving an average period of six and twenty-five hundredths months required for cure for the entire group of 105 patients. Seventy-six patients, 50.7 per cent of the entire group treated or 72 per cent of the 105 cured, were discharged within seven months. This period

TABLE 1—*Number of Patients Cured and Duration of Treatment*

Months Required to Effect Cure	No. of Patients Cured	Percentage of 105 Patients Cured	Percentage of 150 Patients Treated
3	12	11.4	8.0
4	16	15.2	10.7
5	12	11.4	8.0
6	24	22.8	16.0
7	12	11.4	8.0
8	8	7.6	5.3
9	6	5.7	4.0
10	6	5.7	4.0
11	3	2.8	2.0
14	3	2.8	2.0
Totals	105		70.0

TABLE 2—*Relationship of the Number and Size of Lesions to Duration of Treatment Before Recovery*

Group	Extent of Lesions	No. of Patients Treated	No. of Patients Cured	Percentage for Group	Average Time for Cure for Group (Mo.)	Improved Less Than 50 Per Cent	Improved 50 to 75 Per Cent	Improved More Than 75 Per Cent
I	One to five small coin-sized lesions	48	48	100	4.8	—	—	—
II	Not more than one fourth of scalp	32	32	100	6.6	—	—	—
III	One fourth to one half of scalp	17	7	41	8.4	2	4	4
IV	More than one half of scalp	53	18	34	8.6	5	20	10

of seven months is chosen because many boys treated with roentgen epilation experienced embarrassment and self consciousness for a similar period as a result of the baldness and irregular growth of hairs. During these months the boys tended to uncover their heads rarely and reluctantly although the tinea infection was long since cured.

Table 2 demonstrates definitely that there was a direct relationship between the number and size of the lesions and the time required to

effect a cure. The 48 patients with a few coin-sized lesions averaged four and eighth-tenths months for cure. In the next group of 32, in whom involvement of the disease was limited to one fourth of the scalp, the time increased to six and six-tenths months for the group. All of the 80 patients in these two groups recovered fully in an average period of five and five-tenths months. As the lesions increased in size and involved more than one fourth or more than one half of the scalp, the average time for recovery increased to eight and four-tenths and eight and six-tenths months, respectively. Seventy patients had the severe form of the disease, and only 25 of them recovered fully in an average period of eight and five-tenths months.

The 45 patients in whom cure was not effected as of the date of writing belong to the third and fourth categories in table 2, in which the

TABLE 3—*Relationship of Age of Patient to Duration of Treatment Before Recovery*

Age (Yr)	No. of Patients	Average Time for Cure (Mo)
1-2	4	3
3	12	7 0
4	20	6 0
5	8	6 5
6	20	7 4
7	4	8 0
8	8	10 0
9	16	6 4
10	4	5 0
11	3	7 0
12	1	4 0
13	2	4 0
14	3	3 0

disease process involved extensive areas of the scalp. Only 7 of these patients showed improvement of less than 50 per cent. Thirty-eight patients showed an improvement of between 50 and 75 per cent, while 14 patients showed improvement of over 75 per cent. Twenty of the 45 patients not cured had been receiving treatment from five to seven months, the other 25 had been treated for a period of seven to nine months. Judging by the rate of their improvement, one would be justified in predicting that some of these patients would recover fully in several more months.

From table 3 one may deduce that in both extreme ages of the group, the youngest and the oldest, the results were somewhat more favorable

than for the rest of the group. In the age groups of 1 to 2 years and 12 to 14 years, the average time required for cure was three to four months. In the largest number of the group, however, ages 2 to 10, the age of the child had no bearing whatsoever on the time required for cure.

Table 4 indicates that the duration of the disease before treatment was started does not influence the length of the period of treatment. A group of 12 patients that had had the disease for nine to twelve months before treatment was started required ten to eleven months to be cured, contrary to the notion entertained by many that patients whose tinea disease was of long standing recover more readily. On the other hand, another group of 8 patients that had had the disease for eight months before treatment was begun required an average of only three and one-half months for a course of treatment. Again it must be pointed out, then,

TABLE 4—*Relationship of the Duration of the Disease to the Time Required to Effect a Cure*

Duration Before Treatment Was Started (Mo)	No. of Patients Cured	Average Time of Treatment (Mo)
1	4	6.0
2	8	5.5
3	34	7.0
4	15	6.7
5	4	8.0
6	8	6.0
7	12	6.3
8	8	3.5
9	8	10.0
12	4	11.0
Total	105	

that the severity and size of the lesions play the principal role in determining the time required for cure.

No unfavorable reactions were encountered from the application of this ointment. Occasionally the patients complained of slight irritation and tenderness of the scalp. These symptoms disappeared after a few days' rest. The ointment caused pronounced scaling of the scalp and gave the normal hairs a bluish gray tinge. The infected hairs were rendered more fragile and were easily broken. Under the Wood light the fluorescence of the diseased areas changed gradually with this treatment from bright green to dull bluish white. Later the hairs were slowly loosened and detached and became mingled in the debris covering the affected areas. When the adherent scales were removed, the underlying areas were observed to have definite thinning out of the diseased hairs.

Gradually the fluorescence in these areas became fainter, and eventually the remaining hairs ceased to give any fluorescence. Planting these hairs repeatedly on Sabouraud's maltose agar slants failed to produce any growth characteristic of *M. audouinii*. In a few weeks normal hairs appeared and gradually filled in the areas that were partially bald.

None of the other topical applications or medicaments employed have given results comparable to the favorable results obtained with the use of this ointment in tinea capitis. In the mild and moderately severe forms of the disease this treatment compares favorably even with treatment with roentgen rays, if one gives proper consideration to the months of waiting for the regrowth of hairs. In the severe forms, however, epilation with roentgen rays was still a more efficient procedure.

CONCLUSIONS

1 Although epilation with roentgen rays is at present the most efficient form of treatment for tinea capitis of the *Microsporon audouinii* type, simple effective therapeutic agents for this disease are definitely in demand.

2 The results obtained with a list of topical applications of old and new fungicides were entirely unsatisfactory.

3 Unfavorable results were obtained with diethylstilbestrol given orally to 60 boys with tinea capitis and with male hormone given orally and parenterally to 50 boys suffering from the same disease.

4 Treatment with an ointment containing 5 per cent salicylanilide in "carbowax 1500" (a mixture of polyethylene glycols having an average molecular weight of about 500) effected a cure in 105 patients of a group of 150 white children with *M. audouinii* infection of the scalp.

5 The shortest period required for recovery was three months, and the longest fourteen months, giving an average period of six and twenty-five hundredths months for the entire group of 105 patients.

6 Eighty patients whose tinea infection was limited to one fourth of the scalp were cured in an average period of five and five-tenths months.

7 Seventy patients had the severe form of this disease, and only 25 of them recovered fully in an average period of eight and five-tenths months.

8 Of the 45 patients that were not cured, 7 showed an improvement of less than 50 per cent. Fourteen of the remaining 38 patients whose disease improved showed over 75 per cent recovery.

9 The severity of the disease, as manifested by the size and number of lesions, was an important factor in determining the rate of recovery.

10 The duration of the disease before treatment was started and the age of the patient had only little bearing on the time required to effect a cure

11 No unfavorable reactions from the use of this ointment were encountered

12 Five per cent salicylanilide in "carbowax 1500" proved superior to all other topical applications and other medications employed in the clinic at Northwestern University in the treatment of tinea capitis. In the mild and moderately severe types of this disease this ointment gave results that compared favorably with results of epilation with roentgen rays. In the severe forms of tinea capitis, however, treatment with roentgen rays was still more efficient.

NOTE—Since this paper was submitted for publication, the author encountered a small number of patients who showed a more violent reaction to the salicylanilide ointment than that described herein. In each instance after several weeks of treatment with the ointment the infected areas of the scalp became swollen, boggy and tender. The clinical picture resembled closely one of a kerion. When this occurred, mild topical therapy was substituted. All the patients with this type of reaction were completely cured within two to three months.

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USE OF VITAMIN A IN THE TREATMENT OF CUTANEOUS DISEASES

Relation to Estrogen and the Vitamin B Complex

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VITAMIN A is an unsaturated cyclic alcohol¹ It has been extracted from natural sources and reduced to crystalline form,² and its synthesis has been reported³ The precursors of vitamin A are synthesized only by plants, as far as is known,¹ and these substances, classed as carotenoids, function as photosensitive structures in plants⁴ In the animal kingdom, carotenoids are oxidized to vitamin A, and the vitamin is stored in the body In some fish and mammals tremendous amounts of vitamin A are found stored in the liver and in the intestinal fat⁵ The purpose of these great stores is not known

In the human organism, vitamin A is stored in the liver and carotene, after oxidization to vitamin A, is also stored The conversion of carotene to vitamin A has been assumed to occur in the liver However, it has been shown that in rats carotene can be converted to vitamin A only if it is given orally, after injection no conversion of vitamin A can be demonstrated, nor does the injection permanently cure a vitamin A deficiency⁶ It has been suggested that the intestinal wall may be the site

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1 Present knowledge of Vitamin A in Nutrition, Nutrition Rev 4 67, 1946

2 Holmes, H N, and Corbett, R E Isolation of Crystalline Vitamin A, J Am Chem Soc 59 2042, 1937 Van Dorp, D A, and Arens, J F Biological Activity of Vitamin A Acid, Nature, London 158 60, 1946

3 Milas, N A Synthesis of Biologically Active Vitamin A Substances, Science 103 581, 1946

4 Wald, G The Photoreceptor Function of the Carotenoids and Vitamin A, in Harris, R S, and Thimann, K V Vitamins and Hormones Advances in Research and Applications, New York, Academic Press, Inc, 1943, vol 1, p 195

5 Edisbury, J R, Morton, R A, Simpkins, G W, and Loven, J A The Distribution of Vitamin A and Factor A₂, Biochem J 32 118, 1938

6 Lease, J G, Lease, E J, Steenbock, H, and Baumann, C A The Comparative Physiologic Value of Injected Carotene and Vitamin A, J Lab & Clin Med 27 502, 1941

of this conversion. The vitamin itself is of equal activity in rats whether given orally or by injection, although the type of solvent used for injection may alter the rate of absorption.⁷

Vitamin A is almost completely absorbed from the human intestinal tract under normal conditions.⁸ After a test dose of 200,000 international units of vitamin A, an increase in the blood plasma of 300 to 500 international units occurs in three hours. There seems to be no relation between the maximum increase in the tolerance curve and the previous plasma level.⁹ Normal levels of vitamin A in the plasma are usually considered to be from 70 to 150 international units. While the plasma level may reflect a vitamin deficiency if the level is low, it does not usually indicate the amount stored in the liver. It was observed in rats that the level of vitamin A in the plasma was maintained until the stores in the liver were exhausted.¹⁰ In 5 young men who were given a diet rich in vitamin A for thirty days, and then maintained on a diet extremely low in vitamin A for six months, levels of vitamin A in the plasma kept to their initial maximal levels for the entire period. Physical fitness was not impaired, and the visual threshold remained constant.¹¹

Vitamin A is used more efficiently than is carotene. The absorption of carotene depends on the presence of bile salts and pancreatic lipase in the intestine.¹² About 60 per cent is excreted unchanged from the intestinal tract.⁸ If large amounts are taken, the increase of carotene in the plasma may lead to the clinical appearance of carotenemia. The body seems to be unable to convert an excess to vitamin A and seems to have no mechanism to excrete the excess. The threshold quantity of carrots necessary to produce carotenemia is about 4 pounds (about 1,814 Gm) of raw carrots per week for a period of seven months. After cessation of the carrot diet, the fading of the yellow color begins in two weeks and is complete in about eight weeks.¹³ A baby fed only on the breast milk of its carotenemic mother had the condition in two months.

7 Barlow, O. W., and Kocher, H. Utilization by the Rat of Vitamin A, Administered Perorally and Intramuscularly, *Am J Physiol* **137** 213, 1942.

8 Wald, G., Carroll, W. R., and Sciarra, D. The Human Excretion of Carotenoids and Vitamin A, *Science* **94** 95, 1941.

9 Steigmann, F., and Popper, H. The Influence of Large Doses of Vitamin A upon the Plasma Vitamin A Level, *Am J M Sc* **207** 468, 1944.

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12 Irvin, J. L., Kopala, J., and Johnston, C. G. The Absorption of Carotene from Isolated Intestinal Loops, *Am J Physiol* **132** 202, 1941.

13 Almond, S., and Logan, R. F. L. Carotinaemia, *Brit M J* **2** 239, 1942.

The symptoms associated with carotenemia are usually mild loss of weight and the appearance of yellowness most evident on the palms soles and nasolabial folds Results of the examination of patients with carotenemia by Anderson and Soley¹⁴ suggested that an antagonism exists between carotene and thyroxin In an excessive administration of vitamin A, on the other hand, the symptoms may be acute and severe It has long been known by Arctic explorers and Eskimos that the ingestion of polar bear liver can cause severe illness Symptoms of drowsiness and severe headache may occur within a few hours, and peeling of the skin around the mouth or on the whole body appears in the next twenty-four hours Chemical examination of polar bear livers revealed them to be rich in vitamin A, and it seems likely that this is the cause of their toxicity The livers examined contained about 20,000 international units of vitamin A per gram of wet liver, which would be 7,500,000 units in 3/4 of a pound (about 340 Gm) of liver, presumably enough to cause a reaction¹⁵

Josephs¹⁶ reported the case of a boy of 3 years who had taken about 240,000 U S P units of vitamin A as percomorph liver oil daily since he was 3 months old He showed enlargement of the liver and of the spleen, hypoplastic anemia, leukopenia, advanced skeletal development and sparse coarse hair The vitamin A of the plasma was 1,140 U S P units Most of the symptoms disappeared when treatment with the vitamin A was stopped, the hair became normal in two months, and by the end of six months the composition of the blood was normal However, another child, 8 months old, who had taken 400,000 U S P units daily for four months, appeared normal The mechanism for controlling the level of vitamin A in the plasma may have been impaired in the first instance It would appear that it is the amount of vitamin A which is in circulation, and can thus reach susceptible tissue, which determines the reaction The vitamin A which is stored in the liver seems to be harmless, no matter how large the quantity

From the vitamin A stores in the liver a greater amount disappears than that which is assumed to be needed for normal requirements In the rat enough can be stored in the liver to meet theoretically ordinary requirements for a period of about a hundred years However, vitamin A is lost rapidly with diets deficient in vitamin A For several years Davies and Moore¹⁷ tried to explain this observation It was noted that rats re-

14 Anderson, H H , and Soley, M H Effects of Carotenemia on the Function of the Thyroid and the Liver, *Am J M Sc* **195** 313, 1938

15 Rodahl, K , and Moore, T The Vitamin A Content and Toxicity of Bear and Seal Liver, *Biochem J* **37** 166, 1943

16 Josephs, H W Hypervitaminosis A and Carotenemia, *Am J Dis Child* **67** 33 (Jan) 1944

17 Davies, A W , and Moore, T The Interaction of Vitamins A and E, *Nature*, London **147** 794, 1941

ceiving diets low in vitamin E had much lower reserves of vitamin A than those receiving supplements of vitamin E. Tests of this observation demonstrated that in rats with vitamin E supplements to diets deficient in vitamin A the stores of vitamin A in the liver decreased more slowly than in rats which did not receive the supplement of vitamin E.

It has been shown that tocopherol functions as an antioxidant in the gastroenteric tract to protect carotene and vitamin A.¹⁸ This action depends on the presence of vitamin E in the tract itself, and it gives more protection if it is given at the same time as the vitamin A. Vitamin E also protects parenterally injected vitamin A, and the conclusion is that vitamin A is subject to destruction by the enzymes and oxidants in the intestinal tract both during absorption and as it circulates through the vascular system of the intestinal tract.

The bio-assay of fish oils containing vitamin A is done on rats raised specifically for this purpose. These rats are highly bred so that their growth requirements of vitamin A are fairly constant. Even so, the requirements vary with the basal diet, the season of the year and the amount of vitamin A administered per dose.¹⁹ In human beings the requirements must vary widely, as they cannot be controlled by breeding, nor is the effect of the basal diet known. On the basis of experimental work on animals it would seem that 20 international units per kilogram of body weight is about the minimal requirement to maintain good light adaptation, but as light adaptation is probably a late manifestation of vitamin A deficiency, total amounts of 7,500 to 10,000 international units daily are advised.²⁰

Vitamin A therapy has been of some benefit in certain rare cutaneous diseases which are also of a familial nature, namely, keratosis follicularis,²¹ ichthyosis²² and pityriasis rubra pilaris.²³ In patients with such dis-

18 Hickman, K. C. D., Kaley, M. W., and Harris, P. L., *Covitamin Studies. The Sparing Action of Natural Tocopherol Concentrates on Vitamin A*, *J. Biol. Chem.* **152** 303, 1944.

19 Muller, P., and Reinert, M., *Spectrographic Assay of Vitamin A and the Conversion Factor*, *Nature, London* **157** 876, 1946.

20 Jolliffe, N., and Most, R. M., *The Appraisal of Nutritional Status*, in Harris, R. S., and Thimann, K. V., *Vitamins and Hormones. Advances in Research and Applications*, New York, Academic Press, Inc., 1943, vol. 1, p. 65.

21 (a) Peck, S. M., Chargin, L., and Sobotka, H., *Keratosis Follicularis (Darier's Disease). A Vitamin A Deficiency Disease*, *Arch. Dermat. & Syph.* **43** 223 (Feb.) 1941. (b) Carleton, A., and Steven, D., *Dermatosis Follicularis. A Study of Four Cases*, *ibid.* **48** 143 (Aug.) 1943. (c) Leitner, Z. A., and Moore, T., *Vitamin A and Skin Disease*, *Lancet* **2** 262, 1946. (d) Peck, S. M., Glick, A., Sobotka, H. H., and Chargin, L., *Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease)*, *Arch. Dermat. & Syph.* **48** 17 (July) 1943.

22 Peck, S. M., Glick, A. W., and Chargin, L., *Vitamin A Studies in Cases of Ichthyosis*, *Arch. Dermat. & Syph.* **48** 32 (July) 1943. Rapport, H. G.,

eases the results of plasma levels or of absorption curves do not consistently indicate a deficiency of this vitamin.^{21c} When there is a deficiency of vitamin A, Frazier, Hu and Chu²⁴ have noted that follicular hyperkeratosis occurs most frequently at the time of puberty, when the endocrine glands are active in their effects on the skin. It has also been noted that, in attempting to determine vitamin A deficiency in rats by vaginal smear, the occurrence of estrus produces cornification indistinguishable from that of vitamin A deficiency.²⁵ It has also been observed that estrogens applied to the human scalp cause keratinization about follicles and atrophy of sebaceous glands.²⁶ All these observations suggest that the skin, altered by endocrine imbalance, is peculiarly susceptible and may demand great amounts of vitamin A for normal function. The following report of a case is pertinent in this regard.

REPORT OF A CASE

J S, a woman aged 52 years, first noticed thickening and fissuring of the skin of her palms following severe sunburn when she was 16 years old. Her menstrual periods began at the age of 16 and were regular until the age of 46, when cessation was followed by symptoms of flushing and night sweats. The peeling of her palms recurred each summer and was at times accompanied with patches of roughness of the forearms and scaling of the scalp. All these lesions tended to disappear in the winter.

Six years prior to examination, at the time of the first menopausal symptoms, the scaling lesions did not disappear during the winter, and they have been continually present, despite varied local medication. When she was first seen, in January 1945, she had dry imbricated scaling on her scalp and her hair was dry and sparse. Her palms were keratotic and the finger tips were fissured. There was lichenification of the apposing areas of the buttocks. Flushes were of daily occurrence, but were controlled by estrogens given orally or by injection. In July a 5 cm patch of follicular keratosis was seen on each forearm. Treatment with vitamin A, 100,000 units (Lederle Laboratories, Inc, vitamin A with 20 mg of

Herman, H, and Lehman, E. The Treatment of Ichthyosis with Vitamin A, *J Pediat* 21 733, 1942

23 Brunsting L A, and Sheard, C. Dark Adaptation in Pityriasis Rubra Pilaris, *Arch Dermat & Syph* 43 42 (Jan) 1941. Weiner, A L, and Levin, A A. Pityriasis Rubra Pilaris of Familial Type, *ibid* 48 288 (Sept) 1943. Leitner and Moore.^{21c} Porter, A D, and Godding, E W. Pityriasis Rubra Pilaris and Vitamin A, *Brit J Dermat* 57 197, 1945.

24 Frazier, C N, Hu, C K, and Chu, F T. Variations in the Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty, *Arch Dermat & Syph* 48 1 (July) 1943.

25 (a) Evans, H M, and Bishop, K S. On the Invariable and Characteristic Disturbance of Reproductive Function in Animals Reared on a Diet Poor in Fat Soluble A, *Anat Rec* 23 17, 1922. (b) Burrows, H. The Biological Action of Sex Hormones, London, Cambridge University Press, 1945, p 302.

26 Rony, H R, and Zakon, S J. Effect of Endocrine Substances on the Adult Human Scalp, *Arch Dermat & Syph* 52 323 (Nov-Dec) 1945.

vitamin E), was started. By September the follicular keratosis was discernible on the entire extensor aspect of the arms. The palms were unchanged. The soles have never been affected. In March 1946 her hair was thick and shiny, but the imbricated scaling of the scalp and the keratoderma of the palms were increasing. The vulva and intergluteal regions showed confluent redness and scaling, with definite borders. In June keratotic plugs, resembling nits, could be seen for several inches along the shafts of the hair of the scalp. This patient had been taking vitamin A, 100,000 units daily, for twelve months, but because of the lack of improvement, vitamin D, 100,000 units daily, was added along with ox bile, 3 Gm daily. By August there was intense generalized itching, and the follicles of the trunk, arms and thighs appeared prominent by reason of a halo of pigmentation and a small central plug. Follicular spines appeared on the backs of the phalanges by August 15. The plugs increased in size and number, those on the abdomen and lateral aspects of the thighs reaching 4 mm in diameter, and these were surrounded by induration and inflammation for about 1 cm. Because of the lack of response to orally administered vitamin A and the unquestionable diagnosis of *psoriasis rubra pilaris*, vitamin A was given by injection, 100,000 units in corn oil twice weekly. Improvement was noticeable within ten days, and within one month the follicular plugging had decreased and the skin was more pliable. On November 18 the patient was hospitalized for study. During her hospitalization the following vitamins were given orally each day: A, 200,000 units, E, 200 mg, riboflavin, 10 mg, thiamine, 9 mg, nicotinic acid, 15 mg, pyridoxine, 3 mg, pantothenic acid, 30 mg, inositol, 90 mg, and choline, 90 mg. Tests of hepatic function (cephalin-cholesterol flocculation and sulfobromophthalein sodium), tests of basal metabolism and examination of the blood and urine all gave essentially normal results. There was no family history of a similar disease of the skin.

During the two weeks of hospitalization the condition of the skin at first showed a little improvement, but at the end of the two weeks the follicular plugs had increased in size and the itching returned. On December 4 treatment with vitamin A by injection was again started, 100,000 units twice weekly, the response was evident within a week and continued, until by Feb 21, 1947, the scalp and palms were normal, all inflammation had disappeared and there remained pigmentation about the follicles and some fine follicular spines in the follicles of the lumbar region. A vitamin A tolerance test was done on February 25 and showed a normal absorption curve: fasting results were 200 gammas of carotene, 104 international units of vitamin A, with 250,000 units of vitamin A in percomorph liver oil given orally, in three hours results were 181 gammas of carotene, 506 international units of vitamin A, in five hours results were 179 gammas of carotene, 1,221 units of vitamin A, and seven hours results were 183 gammas of carotene, 560 units of vitamin A. Because of the evidence of normal absorption of vitamin A as percomorph liver oil, it was decided to test the clinical response to this preparation. Two hundred thousand units of vitamin A, as percomorph liver oil, had been taken for the last month prior to the date of writing, with little change in the eruption and no signs of improvement.

COMMENT

Consideration of two factors in this case point to a relationship between the patient's endocrine status and the utilization of vitamin A.

- (1) Vitamin A in doses of 100,000 units daily (700,000 units per week)

did not deter the development of extensive pityriasis rubra pilaris in a patient who had had minimal signs of this disease for thirty-six years. Vitamin A was quickly effective when it was given parenterally in doses of 200,000 units per week. That the patient's absorption of vitamin A was not defective was shown by the vitamin A tolerance curve. The vitamin A which entered the peripheral circulation, circumventing the influence of the liver, appeared to be more effective than that which first passed through the liver. (2) This patient was observed each week during a period of eighteen months. Synthetic estrogens were given orally and parenterally to control her symptoms of flushing and night sweats, and during this time the signs of pityriasis rubra pilaris steadily increased.

It can be assumed that in this patient administration of estrogen produced an accentuated need of the skin for vitamin A. The oral dose may have been too small, or it may have been rendered less effective during its passage through the liver. Estrogen is known to affect the function of the liver, particularly in regard to the vitamin B complex,²⁷ and it is possible that the vitamin A was in some way also affected. Conversely, vitamin B complex is necessary for the liver to inactivate estrogen. This might account for the efficacy of the parenterally administered vitamin A, which would escape the portal circulation of the liver. Although no clinical signs of vitamin B deficiency were noticed in this patient, it is not unlikely that such a deficiency did exist.

Of more general interest, however, is the question of the relation of vitamin B deficiency to vitamin A deficiency at the time of puberty. Varied opinions are held in regard to designating phrynoderma as evidence of vitamin deficiency,²⁸ and it is felt that other factors, aside from the deficit of vitamin A, determine whether or not the changes of follicular hyperkeratosis and xerosis will appear. Frazier, Hu and Chu²⁴ suggest that when the sex hormones begin to influence the skin during puberty the cutaneous changes of vitamin A deficiency make their appearance. From the reports of cases of nutritional surveys made in India,²⁹ Africa,³⁰ Malay³¹ and China,³² it is evident, from the descriptions of angular

27 Biskind, G., and Biskind, M. C. The Nutritional Aspects of Certain Endocrine Disturbances, *Am J Clin Path* 16 737 (Dec) 1946

28 Bicknell, F., and Prescott, F. The Vitamins in Medicine, ed 2, New York, Grune & Stratton, Inc., 1946, p 65

29 Alroyd, W. R., and Rajagopal, K. The State of Nutrition of School Children in South India, *Indian J M Research* 24 419, 1936

30 Nicholls, L. Phrynoderma. A Condition Due to Vitamin Deficiency, *Indian M Gaz* 68 681, 1933

31 Fasal, P. Clinical Manifestations of Vitamin Deficiencies as Observed in the Federated Malay States, *Arch Dermat & Syph* 50 60 (Sept) 1944

32 Frazier, Hu and Chu²⁴ Reiss, F. A Contribution to the Cutaneous Manifestations of Vitamin A Deficiency, *Chinese M J* 50 945, 1936

stomatitis, cheilosis and beriberi and from the lists of diets, that these patients were, for the most part, also deficient in the vitamin B complex Biskind and Biskind²⁷ have shown that when a vitamin B deficiency is present, the liver is unable to inactivate estrogen. The estrogen appears in excess in the circulation, but the inactivation of androgen continues, so that an estrogen-androgen imbalance results. Estrogen effects on the skin and vaginal mucosa are similar to the changes seen in vitamin A deficiency.³³ The circulating estrogen may act on the epithelium either by direct antagonism to vitamin A or by increasing the metabolic need of the cells for vitamin A. If such be the case, then a deficiency in the B complex may be the deciding factor as to whether or not the signs of phrynoderma and xerosis appear, and the time of their appearance at puberty is explained. No explanation of the antagonism between estrogen and vitamin A in the skin or vaginal mucosa is apparent from the evidence presented here.

This sequence of events may occur to some degree in such diseases as keratosis follicularis and pityriasis rubra pilaris and thus account for the inconsistent observations in tests for vitamin A deficiency in plasma levels and dark adaptation and may also account for the inconsistent improvement during vitamin A therapy. A better evaluation of this theory might have been possible had the histories been more detailed in regard to the endocrine status of patients with these diseases.

ABSTRACT OF DISCUSSION

DR. MAXIMILIAN E. OBERMAYER. Dr. Keddie's study is a valuable contribution to the complex problem of vitamin A therapy, for it deals with and suggests an explanation for the inconsistencies of response which have puzzled every dermatologist.

The assumption of a relation of a deficiency of vitamin A to that of the B complex vitamins appears logical. Not only do Dr. Keddie's observations and those of other investigators point in that direction, but it has become almost a dictum that deficiency in a single vitamin hardly ever occurs, in most vitamin deficiencies there is a co-existence of deficiency in one or several other vitamins. This is the case in pellagra and in scurvy, in which the development of hyperkeratotic follicular papules is often observed in the earliest changes and points toward a co-existent deficiency in vitamin A, a similar situation evidently prevails in the so-called vitamin A deficiencies.

An even more important point is the alleged and yet unsolved relation of vitamin A to the sex hormones. If the two substances are either antagonistic or, as Dr. Keddie has suggested, an excess of hormones increases the requirements of vitamin A to a considerable degree, there would be an explanation for some

33 Evans and Bishop^{25a} Bullows^{25b} Rony and Zazon.²⁸

of the so far poorly understood observations, as in the observations of deficiency in vitamin A with the formation of follicular hyperkeratoses in pregnancy reported by Rucketts (*Am J Obst & Gynec* 38 484, 1939)

It also seems significant that in true vitamin A deficiency, as well as in acne vulgaris, the maximal degree of follicular hyperkeratosis is present during adolescence. Thus, the degree of sexual development appears to be the critical factor in the response of the pilosebaceous structures to a deficiency of vitamin A.

On the other hand, it is difficult to explain, on that basis, the effect of vitamin A in the prevention and treatment of the precancerous degenerative cutaneous changes, such as keratoses, for these conditions ordinarily occur at a time in life when the production of sex hormones is diminished.

Nevertheless, the known fact that estrogen and a deficiency in vitamin B complex affect the function of the liver is important in attempts to explain the inconsistencies of therapeutic response, because this is in correlation with the results of experimental studies by British and South African investigators on the causal connections between hepatic damage and hypersensitivity to light.³⁴ Such hypersensitivity could, for example, be brought about by damaging the liver through ligation of the common duct. Further studies led to the surprising discovery that absence of a substance which accompanies vitamin A is the critical factor in causation of the hypersensitivity. It has long been known that hepatic cells always contain vitamin A, which is necessary for their normal function. The toxic influence of thyroxin, which leads to the disappearance of glycogen from the liver, can be successfully counteracted by the administration of vitamin A. It is now thought that in the presence of hepatic damage a toxin, probably of intestinal origin, which has escaped destruction in the liver, is activated by sunlight and that treatment successfully directed against the cause of the injury to the liver would eliminate the consequences of hypersensitivity to light. Actually, some British investigators have successfully employed injections of highly refined preparations of natural vitamin A esters containing the active factor which always accompanies such esters in nature. Their work substantiated the theory that it is the absence of this active factor, rather than the disappearance of vitamin A itself from the hepatic cells, which is responsible for the hypersensitivity to light.

By these observations the importance of the connection between damage to the liver and vitamin A metabolism gains new significance, for such damage, sufficient to disturb the process of utilization of vitamin A, may be brought about in many different ways and yet go undetected by present day methods of testing the function of the liver. A disturbance in the balance of the sex hormones, with subsequent dysfunction of the liver and poor utilization of vitamin A, may perhaps be one of the causal factors in acne vulgaris. It is interesting to speculate whether dysfunction of the liver from other causes might be responsible for the tendency to premature degeneration of the skin and the formation of precancerous keratoses, a process in which long-continued exposure to light plays a decisive role. If such correlation were established, a logical explanation for the alleged effect of vitamin A in these disorders would have been found.

One may hope that further studies will be carried out in this direction so that the whole problem of the practically all-important question of pathogenesis of precancerous keratoses may be clarified and practical modes of treatment established.

34 Adler, A. Solar Dermatitis in Adults, *Proc Roy Soc Med* 36 284, 1943

In the meantime I should like to point to the therapeutic effect of the administration of vitamin A in patients with cutaneous diseases characterized by excessive keratinization not limited to the follicular system, that is, calluses, corns, keratoderma and, particularly, common inflammatory dermatoses, such as dry neurodermatitis, which in themselves would not be considered suitable for treatment with vitamin A were it not that some patients have lesions which show an abnormal degree of keratinization and a complete lack of response to standard methods of treatment. In such disorders the administration of vitamin A is of value, but it is highly doubtful that a true deficiency of vitamin A exists. It is likelier that the vitamin, and/or the substances which accompany it, acts as a specific remedy for cutaneous changes, whatever the cause, which are characterized by excessive keratinization.

LICHEN URTICATUS SYNDROME

As a Manifestation of Sensitivity to
Bites from Various Species of Arthropods

LEON GOLDMAN, M D
CINCINNATI

LICHEN urticatus is probably one of the least understood of the cutaneous diseases of childhood,¹ or, in the words of Walter Highman,² "a not very well defined disease of childhood" Howard Fox¹ added that "the disease originally described by Bateman³ in 1813 has been the source of much confusion, which even persists to a degree at the present time"

At present, lichen urticatus is assumed to be a type of hypersensitive cutaneous reaction of unknown causation. In the literature⁴ various factors have been considered, with the variety extending from teething to psychosomatic disturbances. However, there are some definite clinical aspects: first, the clinical picture of the development of the lesions and, second, the seasonal variation. This seasonal variation occurs usually in summer and early fall. The persistent forms of lichen urticatus may last through the winter. It is my impression that the disease in cases observed in clinics in London, England and in Mexico is much severer and more frequent (?) than the disease in cases seen in the United States. Cutaneous testing in patients with lichen urticatus has revealed nothing of value. Cooke⁵ indicated that testing gives practically no assistance, since, in his opinion, reagents play little or no demonstrable part in the mechanism. Cooke⁵ expressed the belief that when reactions are obtained, they are from the associated atopic disorders and have no "direct demonstrable bearing on the symptoms under investigation"

From the *Department of Dermatology and Syphilology of the College of Medicine, University of Cincinnati

1 Fox, H. Diseases of the Skin in Infancy and Childhood, New York, D Appleton and Company, 1930, chap. 16

2 Highman, W., cited by Fox¹

3 Cited by Fox¹

4 Winkler, 2 Strophulus, in Jadassohn, J. Handbuch der Haut und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, p. 326

5 Cooke, R. A. Allergy in Theory and Practice, Philadelphia, W. B. Saunders Company, 1947, p. 497

Walzer⁶ indicated that atopy is significant . . . "about 47 per cent of the patients had positive atopic histories" It is curious that in the search for the elusive antigenic factor antigens from insects and the like have not been considered more strongly, since such antigens have been used in allergic conditions⁷ Parents have suggested frequently that bites from mosquitoes and chiggers had initiated the episodes of lichen urticatus

Bateman⁸ in 1814 wrote, "It may be called lichen urticatus, as its first appearance is in irregular inflamed wheals, so closely resembling the spots excited by the bites of bugs or gnats as almost to deceive the observer" Jonathan Hutchinson³ is reported to have indicated that the disease may be produced by bites of insects In their discussion on lichen urticatus, Ashby, Wright, Ashby and Roberts,⁹ wrote that "in some children fleas and other insects will produce vesicles as well as papules and give rise to more or less constitutional disturbance" In Mexico, Latapi¹⁰ insisted on the reaction from insect bite as the cause of lichen urticatus He has demonstrated to me such cases caused by bites, especially of the bedbug and the flea

Some time after the study reported herein was started, the detailed work of Dietrich¹¹ in Vienna was found He observed the reaction to the actual bite, "Stichversuchen," of cimices and fleas (*Pulex irritans*) Of 31 young children with lichen urticatus, 16 had severe (hypersensitive) reactions to cimex bites, and 30 presented severe reactions to flea bites The lichen urticatus reaction in 21 of these patients was actually caused by fleas, in 3 by cimices, and in 7 by both cimices and fleas

Twenty-nine cases of lichen urticatus from the dermatologic clinic of Children's Hospital and from private practice have been studied since 1941 In 11 of these 29 cases there was a definite atopic background In all except 4 cases the eruptions began in late spring and in summer months In 4 cases the eruptions began in January, September, October and November, respectively Three of the patients of this group of 4 were definitely atopic, and in the fourth patient the

6 Walzer, cited by Andrews, G C Diseases of the Skin, Philadelphia, W B Saunders Company, 1938, p 169

7 Vaughn, W T Practice of Allergy Entomogenous Allergy, St Louis, C V Mosby Company, 1938, p 763

8 Bateman, T A Practical Synopsis of Cutaneous Diseases, ed 3, London, Longman, Hirst, Rees, Orme & Brown, 1814, p 13

9 Ashby, H, Wright, G A, Ashby, H T, and Roberts, C B Diseases of Children Medical and Surgical, London, Henry Frowde & Hodder & Stoughton, 1922, p 675

10 Latapi, F Personal communications to the author

11 Dietrich, A Hautreaktionen nach Ungezieferstichen unter dem Bild eines Lichen urticatus, Arch f Dermat, u Syph 182 668, 1942

lichen urticatus followed scarlet fever at the age of 8 months and persisted for over a year. Two cases of lichen urticatus of the same degree occurred in twins, who were not identical. In 5 patients of the total series, the lichen urticatus definitely followed a reaction to bites in the skin. There was no atopic background in 4 of these persons. The bites were seen by a physician from the onset, and the course of the lichen urticatus which followed was typical. The insects incriminated in the reactions to bites were the mosquito (species?) in 2 cases, the "chigger" (*Eutrombicula*) in 1 case and the cimex in 2 cases. In 4 patients (3 of these were nonatopic) bites were said by the mother to have started the lichen urticatus, but at the time of examination there was no evidence of any primary reaction to bites. In these 4 patients, then, the reaction can be considered as being to bites from types of arthropods, that in 9 of the 29 patients the probable cause was a reaction to bites of insects and the like. In only 1 of these 9 was the lichen urticatus of a prolonged type of reaction, lasting more than a year. In this patient, the reaction to the bite was described by the mother, so that the case was not considered as of a definite type. Only one third of the patients of this series of 29 had detailed cutaneous testing. A wide variety of positive reactions was obtained, and in none of these were the reactions of any definite value. This supports the contention of Cooke.⁵ In 3 patients, cutaneous tests were done with common fly antigen, and in these 3 patients the reactions were negative. No cutaneous testing was done with insect antigens, even in the patients with the "definite" reactions to bites. In several of the patients in whom there was no history of bites, the mother insisted that the patient's going out into the grass would always start this seasonal eruption. Reactions to cutaneous testing, both intradermal and patch testing, with grass antigen were equally negative in these patients. One of the cases of the group in which a "definite" bite had been established was of familial infestation with cimex. The typical bites from cimices were seen on the 3 adults in the family, and the young child of 6 years of age presented, after his typical bites, a generalized, severe and resistant lichen urticatus type of reaction. In the homes of 4 of the children of the group without "definite" reactions to bites, there was detailed employment of insecticides and repellents. These procedures had no effect on the development of new lesions.

Familial scabies was studied in 4 infants and young children, with the possibility that some of the lesions may have been reactions of sensitivity, lichen urticatus type, rather than extension of scabietic lesions. The confusion in the differential diagnosis between scabies and lichen urticatus is well known. These 4 patients were studied in as much detail as is possible in a young child with a generalized

pruritic eruption. Parasites of scabies were isolated from lesions of the extremities, especially from the hand, but lesions on the trunk revealed no parasites. No biopsies were done, however. In 1 child the urticarial lesions were seen preceding the development of the papules. The widespread distribution of the cutaneous lesions of scabies in the young child is well known. Moreover, there may be cutaneous allergy in scabies in the form of associated urticaria and angioneurotic edema. It is suggested, without any definite proof whatsoever, that some of the lesions may be an allergic type of response rather than a direct extension of the lesions of scabies. In 1 child an attempt was made to limit the benzylbenzoate and dichlorodiphenyltrichloroethane (DDT) therapy with bandages only to the hand. However, the general improvement of the child could not be explained entirely as an effect of the treatment on the so-called "primary lesions."

It is suggested also that some of the dermatitis occurring on the back of the neck in children with pediculosis capitis may not always be a bacteride due to the secondary infection or a direct extension, or "toxic" dermatitis or even dermatitis from treatment, but may actually be a type of "localized" lichen urticatus reaction.

In the regions of onchocerciasis in Mexico, reactions to simulium bites were seen in children with typical lichen urticatus reactions.¹² The reactions to bites were studied. Although some persons would present onchodermatitis associated with their reactions to bites, yet other patients would show negative cutaneous results for microfilariae, and it was assumed that their lichen urticatus reaction developed from the bite of the simulium.

No critical studies have been done in this series to explain the persistency of the lesions in lichen urticatus. It would certainly be well to repeat the studies¹³ of the development of the lesion of lichen urticatus with biopsies from the initial urticarial phase to the late infiltrated papular reaction. The histologic picture of the difference between the urticarial reaction and the more infiltrated lesion in lichen urticatus may explain some of the persistency of the lesion. The cellular infiltrate is more intense, the vascular damage is severer and the itching reaction, of course, is more prolonged in the lichen urticatus reaction. Similarly, there is more opportunity for secondary infection of the lesions, because of the persistency of the reactions. In 1 patient of this series of 29, definite and casual psychosomatic factors were observed to help to establish the chronicity of the lesion. In none of the older children followed so far, since 1941, has there

¹² Goldman, L., and Figueroa Ortiz, L. Types of Dermatitis in American Onchocerciasis, *Arch. Dermat. & Syph.* **53**: 79 (Feb.) 1946.

¹³ Fricboes, W. *Grundriss der Histopathologie der Hautkrankheiten*, Leipzig, F. C. W. Vogel, 1921, p. 18.

been any suspicion of the development of true chronic prurigo lesions. In several of the atopic patients of this series the concomitant appearance of definite flexural lichenified areas together with the lichen urticatus were observed. Insects are more active, of course, in the warm seasons. However, in México, D F, Mexico, no special note was made of any seasonal variations of lichen urticatus.

COMMENT

It is obvious that some (how many?) children with the syndrome which is known as lichen urticatus may initiate this reaction by means of the bites of the common type of insects and allied species. The determining factors in these children which produce a generalized allergic response of fairly long duration instead of a primary localized bite type of reaction are certainly not known. Dietrich's¹¹ work with severe reactions to bites of cimices and *P. irritans* in lichen urticatus does tend to prove the concept of hypersensitivity in those particular young children with lichen urticatus. His few experiments, likewise, with the young infants showed that hypersensitivity may be acquired after repeated bites. Similarly, hyposensitization may be accomplished also by repeated bites. Dietrich¹¹ expressed the belief that lichen urticatus no longer occurs when decided decrease in sensitivity to the bites is shown. It seems that it would be possible also to study the lichen urticatus type of response critically by means of appropriate antigens of insects involved. It is curious that in only 2 patients of the group of 9 possible reactors to insect bites was the reaction repeated one more season. In some extremely sensitive patients it may not be necessary to have the actual bite of the insect, but even perhaps endogenous sensitization by means of the emanation or so called "dust" or debris of the insect.

It is apparent that at the present time the diagnosis of lichen urticatus as a reaction to bites from arthropods can be made only by the definite personal observation of the primary reaction to the bite followed by the dissemination of the characteristic eruption after the primary bite and the actual presence of the insect, when such insects as the cimex, pulex and the pediculus are suspected. The presumptive diagnosis may be made by the observant parent, although this is not reliable. The reaction to insect bite was observed to occur during the spring-summer season and was usually in nonatopic persons. Only critical work with detailed testing, both with prepared antigens and with the actual bite, and observation in a controlled environment will help to elucidate some of the confusion of the syndrome of lichen urticatus.

When bites from insects and the like are suspected in young children with lichen urticatus, detailed search for these offenders

should be made With modern advances in the chemical control of insects, repellents, especially "NMRI 448" (contains 70 per cent 2-phenyl cyclohexanol and 30 per cent 2-cyclohexyl cyclohexanol), and insecticides, such as dichlorodiphenyltrichloroethane (DDT), octachloro-4,7-methanotetrahydroindane (chlordane or "velicol 1068") and gamma isomer of 1, 2, 3, 4, 5, 6 hexachlorocyclohexane, should be used efficiently before the older technic of change in environment is advised However, detailed toxicologic studies of the newer insecticides are still needed

SUMMARY AND CONCLUSIONS

Of 29 patients with lichen urticatus, definite history and observation of reaction to bites from various species of arthropods as initiating the syndrome was observed in 5 patients and presumptive evidence in 4 patients These reactors to bites belong, as a rule, to the non-atopic group of patients with lichen urticatus Personal observations in Mexico have established the fact also that bites from insects and the like may initiate the syndrome of lichen urticatus The insects incriminated included the fly, chigger, mosquito, flea, cimex and simulum It is suggested that in some cases of scabies in infants and children a "portion" of the generalized reaction may be a sensitivity response rather than a dissemination of actual infective lesions Detailed testing with antigens and with the actual insect bite (Dietrich), analysis and environmental control may help to determine the significance of the role of sensitivity from bites of insects and the like in children with the lichen urticatus syndrome

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Clinical Notes

TREATMENT OF FAMILIAL BENIGN CHRONIC PEMPHIGUS

Rapid Improvement with Penicillin Therapy

C C Carpenter, M D, Summit, N J

The reports that have been published concerning the treatment of familial benign chronic pemphigus are, for the most part, discouraging

Because of the repeated observation of the staphylococcus¹ and the occasional presence of short-chained streptococcus^{1b} in the vesicles, bullae and crusts characteristic of this affliction, the use of local antiseptics has been the most popular therapeutic approach. Beneficial effects have been noted from the local applications of ammoniated mercury ointment in 1 per cent to 3 per cent concentration,² boric acid ointment^{2b} and mildly antiseptic wet dressings, including alibour water (water containing zinc and copper sulfates)². Superficial roentgen therapy has been successful in some patients,³ but in others has proved ineffective.⁴ Ultraviolet irradiation produced no improvement in a patient treated by Lynch.^{1d}

In an endeavor to achieve more permanent results, many types of internal therapy have been tried. The intravenous injections of *Staphylococcus aureus* vaccine combined with low power roentgen ray therapy kept a patient of Ayres and Anderson^{1b} free of lesions for a year. Subsequent recurrences in this same patient could be controlled by repeated intravenous injections of a combined *Staph aureus* and *Streptococcus viridans* vaccine. However, an autogenous streptococcus vaccine did not help a patient of the Haileys.^{2b} Lynch^{1d} was able to obtain complete healing in his patient with the administration of sulfathiazole for ten days. The value of treatment with this drug is supported by Pinkus and Epstein,⁵ who achieved a rapid remission in 1 of their patients with sulfapyridine. High dosage vitamin A therapy has been reported as being useful in 1 patient⁵

1 (a) Pels, I R, and Goodman, M H. Criteria for Histologic Diagnosis of Keratosis Follicularis (Darier), *Arch Dermat & Syph* 39 438 (March) 1939 (b) Ayres, S, Jr, and Anderson, N P. Recurrent Herpetiform Dermatitis Repens, *ibid* 40 402 (Sept) 1939 (c) Becker, S W, and Obermayer, M E. Bullous Disease. Bullous Darier's Disease (Pels and Goodman), *Familial Benign Pemphigus* (Hailey and Hailey), *Herpetiform Dermatitis Repens* (Ayres and Anderson), *ibid* 41 1170 (June) 1940 (d) Lynch, F W. Benign Pemphigus (Hailey and Hailey) Treated with Sulfathiazole, *ibid* 43 736 (April) 1941

2 (a) Ayres and Anderson^{1b} (b) Hailey, H, and Hailey, H. *Familial Benign Chronic Pemphigus*, *South M J* 33 477 (May) 1940

3 (a) Ayres and Anderson^{1b} (b) Anderson, C R, in discussion on Ayres, S, and Rogers, J D. Recurrent Herpetiform Dermatitis Repens, *Arch Dermat & Syph* 42 490 (Sept) 1940 (c) Hopkins, J G. *Familial Benign Chronic Pemphigus*, *ibid* 51 69 (Jan) 1945

4 (a) Lynch^{1d} (b) Hailey and Hailey^{2b} (c) Montgomery, R M. *Familial Benign Chronic Pemphigus*, *Arch Dermat & Syph* 50 53 (July) 1944

5 Pinkus, H, and Epstein, S. *Familial Benign Chronic Pemphigus*, *Arch Dermat & Syph* 53 119 (Feb) 1946

and ineffective in another ^{4c} Anderson^{3b} and Frost⁶ expressed the belief that intravenous injections of calcium are beneficial in lessening the eruptive tendency. Among the other internal remedies that have been tried, and which only temporarily altered the progression of this disease, are injections of neoarsphenamine, bismuth compound,^{1a} trichophytin,^{2b} snake venom, extract of liver, arsenic compound and vitamin K ^{3c}

In the general management of patients with this cutaneous disease, Frank and Rein⁷ stressed the importance of avoiding superficial trauma, to prevent recurrences, and Montgomery^{4c} noted that a change to cooler atmospheres hastened recovery.

As this eruption has been frequently considered to be a form of dermatitis herpetiformis,⁸ I thought that penicillin therapy might possibly be of value.⁹

REPORT OF CASES

CASE 1—W L, a white man aged 39 years, first came under my care in 1932, because of a recurrent cutaneous eruption on the shoulders, neck, axilas and scrotum, which had been variously diagnosed as bullous impetigo and fungous infection. His father had a mild form of this disease all his life, and 2 sisters were known to have had similar cutaneous manifestations.

Except for the recurrences of this eruption, beginning at the age of 19, his general health had been good. However, there have been mild recurrences of epidermophytosis of the feet. All laboratory examinations, including repeated complete blood cell counts, urinalysis, glucose tolerance test, tests of sedimentation rate and complete chemical content of the blood and Wassermann and Kline tests, have always yielded normal values. The disease, from a biopsy in 1937 (first examination by the late David Satenstein) was considered to be a form of Darier's disease. Dr. Wilbert Sachs reviewed the slide at that time and expressed the belief that it presented observations consistent with epidermolysis bullosa. A subsequent review of the same section in 1942, by Dr. P. A. O'Leary and Dr. H. Montgomery, resulted in agreement on a histologic diagnosis of familial benign chronic pemphigus.

During severe exacerbations of the cutaneous disease in 1937 and 1938, he was seen in consultations with the late Dr. H. J. F. Wallhauser and Dr. G. M. MacKee. The former stated the belief that the patient had an unusual form of epidermolysis bullosa and the latter an aberrant form of pemphigus.

It was consistently observed that this patient was generally worse during the hot summer months, but would also have recurrences in the winter while playing ice hockey. He blamed the wearing of a jockstrap for the formation of new scrotal lesions, and on several occasions new bullae were observed at the cutaneous sites that had been hit by a hockey stick or puck. New lesions on the front of his neck had been produced by the irritation from shaving.

During his naval service in 1944, while he was serving in the heat and humidity of the South Pacific area, a severe exacerbation developed. It was not until

⁶ Frost, K, in discussion on Ayres, S, and Rogers, J. D. Recurrent Herpetiform Dermatitis Repens, Arch. Dermat. & Syph. 42:490 (Sept.) 1940.

⁷ Frank, S. B., and Rein, C. R. Dyskeratoid Dermatoses, Arch. Dermat. & Syph. 45:129 (Jan.) 1942.

⁸ Ayres and Anderson ^{1b} Anderson ^{3b} Pinkus and Epstein ⁵

⁹ Carpenter, C. C., and Hall, W. H., Jr. Treatment of Dermatitis Herpetiformis with Penicillin, Arch. Dermat. & Syph. 51:241 (April) 1945.

he was returned to the cooler climate of a naval hospital in Northern California that any form of local therapy was successful

From 1932 to 1934 his cutaneous lesions responded satisfactorily to superficial roentgen therapy and the local application of tincture of iodine, silver nitrate, methylrosaniline chloride, alibour water and "quinolor compound ointment" (contains 10 per cent benzoyl peroxide and 0.5 per cent "quinolor" [a mixture of 8-hydroxyquinoline] in a base of equal parts of petroleum and wool fat). At that time he was observed to be hypersensitive to staphylococcus vaccine and was given gradually increasing dosages of staphylococcus toxoid. He remained free of all lesions for a year following this desensitization, and since that time has received three such series of injections, which were successful in suppressing all but minor manifestations for periods varying from seven months to two years. Sulfathiazole was given orally in 1941 for a period of five days, with only moderate success.

In February 1947, this patient returned after an absence of five years. There was minor activity of the cutaneous lesions in his axilla, neck and scrotum, that had been present since the previous summer. Penicillin was given orally, 25,000 units every three hours until 1,500,000 units had been taken, and local therapy was confined to the use of petrolatum. An immediate decided improvement was noted, and all lesions except the most deeply fissured had healed within a week. Subsequent local applications with penicillin ointment and tyrothricin (solution) did not effect any further improvement. Another severe outbreak occurred during the heat of June, and the patient was hospitalized. Combined treatment, with the injection and oral administration of 200,000 units of penicillin daily and the local use of penicillin, 1,000 units per gram of hydrophilic ointment base, produced complete healing of all lesions within five days.

CASE 2—C. L., a white housewife aged 42 years, a sister of the patient in case 1, was seen in January 1947, complaining of a spreading annular eruption on the right shoulder. This was the first manifestation of this cutaneous disease on the glabrous skin, but during the past several years there had been a recurrent fissuring of the anal mucosa, which was believed to be a part of this same disease. Because of the family history, as well as the fact that these fissures had always healed promptly with local antiseptic therapy, no further investigations had been made. Her general health had otherwise been good.

The present eruption had begun ten days previous to examination and was the result of friction produced by a tight bathing-suit strap, worn while on a vacation in Florida. It had started as a small "blister" and had spread eccentrically, in spite of daily applications of a sulfadiazine ointment. When first observed, the area was 2 inches (about 5 cm.) in diameter and had an irregular border of vesicles, bullae and pustular crusts on a raw oozing base. The healed center area was pink and had a superficial scale.

Treatment was started with two daily applications of an ointment containing 500 units of penicillin per gram of hydrophilic ointment base. As a result, the eccentric progression of the border was stopped and the crusted areas healed, but the vesicles and bullae did not disappear. Following this, wet dressings containing 0.3 mg. of tyrothricin per cubic centimeter of distilled water were applied, but the vesicular edge continued to advance. Oral penicillin therapy, with the ingestion of 25,000 units every three hours, was then recommended, with local therapy limited to daily applications of petrolatum. Within four days, and after 750,000 units had been taken, the vesicles and bullae had entirely disappeared, and the involved area of skin had remained entirely well as of the time of writing.

SUMMARY

It has been verified that trauma to the skin and hot weather are predisposing factors in the recurrence of familial benign chronic pemphigus

It is agreed that some form of desensitization with straphylococcus vaccine or toxoid is helpful in producing remissions of this disease

Combined internal and local therapy with penicillin is of value in controlling exacerbations

129 Summit Avenue

SEVERE REACTIONS TO PENICILLIN

H H SAWICKY, M D

AND

CHARLES R REIN, MD
NEW YORK

The oral and topical use of penicillin, in such forms as tablets, lozenges, troches, wet dressings, ointments, sprays and nose and eye drops in the treatment of comparatively minor ailments may sensitize many persons to this valuable antibiotic. Two severe sensitization reactions to penicillin are reported

REPORT OF CASES

CASE 1—S B, a white man aged 57, consulted us on July 16, 1946, for chronic furunculosis of ten months' duration. He denied a history of active fungous disease and a personal or family history of allergy. In October 1945, he noted numerous furuncles on his upper extremities. Penicillin ointment was prescribed in November, and, after three weeks of use, an erythematous edematous eruption appeared on the face and neck. The eruption soon became generalized, necessitating hospital care for three months. On July 16, 1946, 300,000 units of penicillin in peanut oil and wax (Romansky formula) was administered intramuscularly for a recurrence of the furunculosis. Within thirty minutes following the injection, the patient presented the picture of "anaphylactic shock." He was apathetic and complained of severe headache, coldness, nausea, vomiting and shaking chills. His face was pinched and his skin pale, with dusky cyanosis of the lips, tip of the nose and ear lobes. His temperature was subnormal, breathing was shallow and sighing, the pulse was barely perceptible, and the blood pressure was 60 mm of mercury systolic and 0 diastolic. Epinephrine was given subcutaneously and tripelennamine hydrochloride ("pyribenzamine hydrochloride" N N R) administered orally. Within an hour, generalized erythema, edema of the extremities and urticarial lesions on the forehead were noted. The urticaria became generalized and persisted for twenty-four hours, at the end of which time the cutaneous and systemic manifestations of the episode were no longer in evidence.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post Graduate Medical School and Hospital, Dr Marion B. Sulzberger, Director

Abstract of report presented by title at the Conference on Antibiotic Research under the auspices of the Antibiotics Study Section of the National Institute of Health, Washington, D C, Jan 31, 1947

CASE 2—S F, a white married woman aged 31, was seen for the first time on March 22, 1947. She gave a history of the onset of sore throat, pain in the back, cough and malaise, March 6, 1947. She denied a history of active fungous disease and a personal or family history of allergy. Treatment with penicillin tablets, 50,000 units every four hours, was started on March 7, and continued, in an irregular manner, until March 22. Because of the persistence of symptoms and a rise in temperature, 300,000 units of penicillin in peanut oil and wax (Romansky formula) was administered intramuscularly on March 15, 16, 17 and 18. During the night of March 18 there was a decided turn for the worse, and two days later the patient was hospitalized, with a tentative diagnosis of septicemia. Examination on March 22 revealed an acutely ill patient, lying in a fixed position in bed and resisting all movements, active or passive. She complained particularly of pains in the muscles, bones and joints. The temperature was 104 F, the pulse rate 120 and the blood pressure 112 mm of mercury systolic and 75 diastolic. There were generalized giant urticaria, most apparent on the trunk and upper extremities, edema of the upper eyelids and a dusky erythematous edematous scaling eruption on both malar regions. Cervical, axillary and inguinal lymph nodes were enlarged and tender, and the right wrist and right knee joints were hot and swollen. Laboratory observations were as follows: The hemoglobin was 64 per cent, the red blood cell count 3,270,000 and the white blood cell count 21,700, with 81 per cent neutrophils, 13 per cent lymphocytes, 5.5 per cent monocytes, 0 per cent eosinophils and 0.5 per cent basophils. The sedimentation rate (Westergren method) was 57 mm in fifteen minutes, 102 mm in 45 minutes and 114 mm in 60 minutes. Examination of the urine revealed a trace of albumin, the urine was otherwise essentially normal. Results of repeated blood cultures were negative, as was culture of the urine. Culture of material from the throat disclosed *Streptococcus viridans* predominating.

In arriving at a diagnosis of a severe serum-sickness-like reaction to penicillin, it was necessary to consider and exclude septicemia, acute lupus erythematosus and dermatomyositis.

Treatment with penicillin in all forms was discontinued, and tripeleennamine hydrochloride, 100 mg every four hours, was administered. After forty-eight hours, the eruption showed signs of fading and the patient moved about in bed and stated that the joint and bone pains were less troublesome. On March 29, one week after the cessation of penicillin therapy, the patient was out of bed, free from signs or symptoms. She made an uneventful recovery and was discharged from the hospital on April 2.

The following classification of common reactions to penicillin was previously reported¹

- A. Toxic Reactions
 - 1. Intrathecal penicillin reactions
 - 2. Herxheimer reaction } Not peculiar to penicillin but common to all potent
 - 3. Therapeutic paradox } spirocheticides and antibacterial agents
- B. Allergic Reactions
 - 1. Pruritus, urticaria, angioneurotic edema, asthma, serum-sickness-like reaction and anaphylaxis-like reaction (immediate or delayed)
 - 2. Erythematovesicular desquamating type
 - 3. Contact dermatitis type
 - 4. Experimental
 - (a) Arthus type
 - (b) tuberculin type
 - (c) anaphylaxis
 - (d) photosensitization(?)

1 Romansky, M. J. The Current Status of Penicillin Therapy, Veterans Administration Technical Bulletin (TB 10-25), Washington, D. C., Government Printing Office, March 28, 1947.

According to this classification, the condition in case 1 is considered an anaphylaxis-like reaction and in case 2 a serum-sickness-like reaction

The incidence of allergic reactions of all types following the injection of penicillin in peanut oil and wax (Romansky formula) is about 3 to 5 per cent. It is anticipated that the number of such reactions will rise sharply as more patients become sensitized following the oral and/or topical use of penicillin.

GRANULOMA PYOGENICUM

Report of An Unusual Case

KATHLEEN A. RILEY, M D
DURHAM, N C.

Granuloma pyogenicum is seen commonly in dermatologic practice. Since its first description in 1897 by Poncet and Dor¹ it has been well studied and defined. The original and early investigators called this infection "botryomycosis," because of its similarity to a disease occurring in castrated horses. However, the causation is different, and it is now generally agreed that the cause of granuloma pyogenicum is *Staphylococcus aureus*. The term "pyogenic granuloma" as Michelson² described it included "all sharply circumscribed granulation tissue growths occurring on cutaneous or mucous membrane surfaces and having the appearance of a tumor."

Hartzell³ first described this condition in America under the name of granuloma pyogenicum. Wile⁴ in 1910 summarized the literature to that date with a critical comprehensive review. Michelson in 1925 reported a study of 29 cases, with a complete discussion of the disease process. Since that time there have been only a few scattered reports in the literature.

Granuloma pyogenicum is a rapidly growing granulomatous lesion that usually occurs at the site of an injury. It is usually less than 1 cm. in size. However, there are a few reports of lesions as large as 3 or 4 cm. in diameter. It is usually moist, fleshy, mushroom-like and bright red, bluish red or brownish red. At times the surfaces may be ulcerated, presenting a purulent discharge. Granuloma pyogenicum frequently occurs on the hands, arms and face, but occasionally may occur on mucous membranes. However, no part of the body seems to be immune. All ages and both sexes are affected about equally. The subjective symptoms may be insignificant, although hemorrhage is common. Pain, if present, is mild, but itching may be extreme.

The typical histologic picture is that of an infected angioma. Characteristically it is a pedunculated lesion showing numerous capillaries and newly formed vessels densely infiltrated with leukocytes which are predominately polymorphonuclear in character.

From the Division of Dermatology and Syphilology, Department of Medicine, Duke University School of Medicine, Durham, N C.

1 Poncet, A., and Dor, L. Botryomycosis humaine, *Rev de chir* **18** 996, 1897.

2 Michelson, H. E. Granuloma Pyogenicum. Clinical and Histologic Review of Twenty Nine Cases, *Arch, Dermat. & Syph* **12** 492 (Oct) 1925.

3 Hartzell, M. B. Granuloma Pyogenicum, *J Cutan Dis* **22** 520, 1904.

4 Wile, U. J. Granuloma Pyogenicum, *J Cutan Dis* **28** 662, 1910.

The prognosis is usually good if the lesion is completely removed by electro desiccation or freezing. Since the advent of the use of sulfonamide drugs, there have been reports by Allison⁵ and Drummond⁶ of response to systemic administration of sulfathiazole in a dosage of 4 Gm per day. Treatment with roentgen rays has also given excellent results. However, if the lesion is not completely destroyed recurrence is common. I feel that the case presented is such an unusual one that it warrants reporting.



A, appearance of the lesions before treatment *B*, appearance of the chin after treatment

REPORT OF A CASE

L. M. F., a 41 year old white married woman was seen first at Duke Hospital on Jan. 21, 1946 with a chief complaint of a cutaneous eruption on her chin.

5 Allison J. R. Granuloma Pyogenicum Treated with Sulfathiazole. Report of Case. Arch. Dermat. & Syph. 45: 579 (March) 1942.

6 Drummond A. C. Unusually Large Multiple Granuloma Pyogenicum of the Scrotum Treated with Sulfathiazole, Urol. & Cutan. Rev. 47: 515, 1943.

Present Illness—Four weeks previously a hard painful erythematous nodule had developed on her chin. This was surrounded by several similar smaller lesions, all of which contained a small amount of pus. She had been treated with a penicillin ointment, but the lesions had continued to spread.

Family and marital histories were noncontributory.

Physical Examination—On the chin was a cauliflower-like mass of grouped papular lesions, about 5 cm in diameter. The lesions were erythematous, soft, shiny and spotted with crusts and a pustular exudate (*A* of the figure). Except for the presence of the cutaneous lesions, the physical examination revealed the patient to be essentially normal.

Laboratory Observations—The peripheral blood observations were normal, with a hemoglobin content of 13.9 Gm, red blood cells 4,650,000 and white blood cells 11,450; the differential count showed 59 per cent polymorphonuclear cells, 4 per cent eosinophils, no basophils, 10 per cent monocytes and 27 per cent lymphocytes. Kahn, Kline, Wassermann and Mazzini reactions were negative. Culture of the lesion revealed hemolytic and nonhemolytic *S. aureus*. The histologic picture was that of granuloma pyogenicum.

Course—Potassium permanganate compresses (solution of 1 to 4,000) were applied to the chin, one hour three times a day, followed by benzalkonium chloride in solution of 1 to 1,000. The patient was given 10,000 units of penicillin every three hours for the first ten days of hospitalization. She was then given 1 Gm of sulfadiazine four times a day. On the fourth hospital day the entire lesion was electrodesiccated, with the patient under "pentothal sodium" (sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate) anesthesia. After fourteen days the patient was discharged, with the lesion decidedly improved.

The patient was followed up in the outpatient department for six months. During this time several small new papular lesions appeared, and on each return visit they were electrodesiccated and touched with 50 per cent trichloroacetic acid solution. The patient continued to use the benzyltrialkonium chloride on the lesions three times a day and applied penicillin ointment three times a day. The patient also continued to take 0.5 Gm of sulfadiazine four times a day. In June, six months following the onset of the disease, there was no active process and the chin appeared normal except for some erythema at the site of the previous lesions (*B* of the figure).

COMMENT

This patient presents the usual history and course of granuloma pyogenicum. However, it is interesting, because despite the unusually large size and number of lesions a good result was obtained, from a curative as well as from a cosmetic point of view. The patient's chin was not scarred or marred, and no "cover-up" or plastic surgery was required. Ten months after treatment was discontinued there was no recurrence of the lesion.

Obituaries

WILLIAM THOMAS CORLETT, M D 1851 1948

Dr William Thomas Corlett, the oldest living member and honorary member of the American Dermatological Association, Inc., died on June 11, 1948, following a cerebral vascular accident

Dr Corlett was born on a farm in Orange Township, Cuyahoga County, Ohio, April 15, 1854, a son of William and Ann (Avery) Corlett. In his boyhood and young manhood he knew the meaning of hard toil. He was the thirteenth William Corlett in direct descent from his Isle of Man ancestors, family records going back to 1500. He graduated from Chagrin Falls Academy, then entered Oberlin College and received his medical degree in 1884 from Wooster University Medical Department, now a part of Western Reserve Medical School.

He then started the practice of medicine and was named Demonstrator of Anatomy in his Alma Mater. However, he was not satisfied with the outlook and consulted several well known medical men in regard to the postgraduate study of diseases of the skin and syphilology. They all told him that he was crazy, that he would starve to death. Nevertheless, he borrowed money at 8 per cent per annum from an uncle and went to London, studying at the London Hospital, receiving his L R C P (London) at The Royal College of Physicians in 1881, later going over to l'Hôpital St Louis, in Paris, for a period. He studied under such men as Jonathan Hutchinson, Sir Frederick Treves, Tilbury Fox, Stephen MacKenzie and Crocker. He numbered Sir Malcolm Morris among his life-long friends and fellow students.

In 1882 he returned to Cleveland as the first dermatologist in that part of the country. He was named Lecturer in Skin Diseases in the Medical Department of Wooster University and opened the first dermatologic clinic in Northern Ohio. The next year he was made full professor. In 1885 he went to Western Reserve University as lecturer and three years later was made full professor, a chair which he held until his appointment as professor emeritus in 1914. His chair of dermatology and syphilology is one of the oldest west of the Alleghenies. He was appointed visiting dermatologist to various hospitals in Cleveland.

The great smallpox epidemic in Cleveland and Northern Ohio in 1899 and 1900 brought out his highest qualities as a physician and public servant. He was an observant student and saw practically every case

occurring in the Cleveland area and Northern Ohio. Moreover, too little was known of the subject at the time, and he acquired a large collection of photographs of the disease in all its stages. This is the basis on which his monograph on acute exanthemas was based. It was con-



WILLIAM THOMAS CORLETT, M.D.
1854 - 1948

sidered an authoritative volume of its time and received international notice. He was invited to give the annual oration to the Dermatological Society of Great Britain and Ireland in 1903, his address being on small-pox. Through the years he made many return trips to the various

clinics in England and on the Continent, as well as to the Caribbean Sea and the shores of South America and to Hawaii

In 1936 he presented the Corlett Room to the Cleveland Medical Library. Many American and foreign dermatologists are acquainted with this gem containing the bound volumes of current journals on dermatology and syphilology, as well as many other precious volumes of the past devoted to this specialty. The room is also of great interest to medical students and younger dermatologists because of the large number of very creditable oil portraits of American, French, German and English dermatologists and scientists of a past generation. It is a worthy memento of the man to his fellow men.

Despite a busy life in his work and teaching, Dr. Corlett found time to write many articles on his specialty and volumes on various subjects as well. "The Exfoliative Dermatoses" in Morrow's "System of Dermatology," volume 3, 1894, "The Vegetable Parasitic Diseases of the Skin" in Bangs and Hardaway's "American Textbook of Genito-Urinary and Skin Diseases," 1898, "The Acute Infectious Exanthemata," 1901, "Purpura, Pompholyx and Pellagra" in "Reference Handbook of the Medical Sciences," 1903, "Lichen, Lentigo, and Granuloma Annulare" in the 1905 edition of the "Reference Handbook of the Medical Sciences", "The American Tropics," 1908, "The People of Orrisdale and Others," 1917, "Reminiscences," 1920, "Medical Miscellany, Mostly Historical," 1932, "The Medicine Man of the American Indian and his Cultural Background," 1935, and "Afterglow Meditations," 1943, an epic poem in blank verse, composed and published after the death of his beloved wife, Amanda Leisy Corlett, who had done so much in encouraging him through his long career.

In addition to honors showered on him by his local medical societies, Dr. Corlett was a Fellow of the Royal Society of Medicine, Great Britain, and a Corresponding Member of the British Association of Dermatology and Syphilology. He was a delegate to the American Public Health Congress in Mexico City in 1892, a delegate to the International Medical Congress in Rome in 1894 and in London in 1913 and a delegate to the International Dermatological Congress in London in 1896. He was a Fellow of the American Medical Association and of the American Association for the Advancement of Science. He served as Secretary and later as President of the Section on Dermatology and Syphilology of the

American Medical Association and was a member and one time President of the American Dermatological Association, Inc , as well as an honorary member in his later life He was an honorary member of the New York Dermatological Society and served for a long term of years on the editorial board of the ARCHIVES OF DERMATOLOGY AND SYPHIL-
OLOGY In 1943 the honorary degree of Doctor of Humanities was conferred on him by Western Reserve University

His memory will be treasured by his students and revered by his associates and colleagues, but long after the man himself is forgotten his Corlett Room in the Cleveland Medical Library will serve as an inspiration to future generations of medical men and dermatologists

HAROLD N COLE, M D

FELIX PINKUS, M.D.
1868—1947

Dr Felix Pinkus died on Nov 19, 1947, at the home of his son, Dr Hermann Pinkus, in Monroe, Mich. He was born in Berlin, Germany, on April 4, 1868, where he lived and practiced the greater part of his life. Dr Pinkus came to America in 1941 and made his home here until his death.

He attended the universities of Berlin and Freiburg, receiving the M.D. degree from the latter institution in 1893. He showed an interest in comparative anatomy early in his medical career. His graduation thesis was on the subject of the cranial nerves of *Protopterus annectens*, in which he described the *nervus terminalis*, formerly discovered in sharks by the Berlin anatomist Gustav Fritsch, and later verified by others through the whole series of vertebrates, including man.

In his early years he worked in the laboratories of Paul Ehrlich on problems related to diphtheria antitoxin and in the institute of Robert Koch, and he carried on research under Engelmann and Fritsch in the physiologic institute in Berlin.

His dermatologic training included an assistantship in Breslau under Albert Neisser, where he began his work on the normal anatomic structure of the skin, a task which he continued throughout his life. Because of his mastery of that subject, he was asked to write on the anatomy of the skin for Jadassohn's "Handbuch," a truly notable contribution. He also contributed a most remarkable chapter on embryology of the skin for Keibel and Mall's "Manual of Human Embryology." In Breslau he worked on leukemia, a subject in which he was particularly interested, because of his association with Ehrlich, whose early studies on staining the blood he had the opportunity of observing at first hand. Dr Pinkus continued his dermatologic training in Bern, Switzerland, with Jadassohn, and did postgraduate work at the Hospital St. Louis in Paris. He contributed to many medical encyclopedias and wrote a book on the hair and a textbook on dermatology. He also edited a reference book on syphilis.

Dr Pinkus made a hobby of studying the phylogenetic origin, structure and pathologic changes of the hair and nails, and his knowledge of those structures and their diseases was equaled by none. He discovered an organ which he called *Haarscheiben*, a nerve disk, near the hair root, and also a muscle belonging to the hair follicle, which is arranged at right angles to the muscle *arrector pilorum*. He worked out the method

of nail growth by studying the structure of the horse's hoof and was able definitely to demonstrate the likenesses

Dr Pinkus practiced dermatology in Berlin from 1898 to 1938. He was a professor of dermatology at the University of Berlin and for twenty-five years was director of the Reichdorf Women's Hospital. Here he observed, treated and studied syphilis on a material over which he had absolute control. He was one of the first to use Ehrlich's "salvarsan" (arsphenamine) and made one of the first complete studies of arsenical dermatitis, following the use of that drug. It is not necessary to cite his many medical papers. His recognition and description of the disease which is associated with his name, lichen nitidus, is perhaps best known to us. His contributions to medical literature numbered one hundred and fifty.

Dr Pinkus' family came from Silesia and later settled in Berlin. His father established a sales agency for linens, one brother, George, was a chemist, his other brother, Eugene, was a manufacturer of fine surgical instruments. Dr Pinkus' son, Hermann, and his daughter, Luise, are both physicians. There is one surviving grandchild.

His intellectual attainments alone could never have given him the particular characteristics which made him so decidedly different and likeable as a man. They might be summed up as simplicity, an almost childlike innocence, together with great intelligence and integrity. He usually appeared preoccupied, but never seemed to miss anything. Actually, he always listened intently to the conversations and problems of others, and he possessed a sensitivity which made it easy for him to be in accord with the situation at hand. He had artistic ability, so well demonstrated by his color sketches and his keen interest in the creative arts. His crayon illustrations on the black board, when giving a medical lecture, were a delight to his audiences.

Felix Pinkus was noble and gallant, and, although he had encountered many difficulties in his life, he was never self pitying nor vindictive. He was understanding and forgiving. His modesty and retiring nature prevented his seeking many offices and honors which he could have had. In addition to his membership in the Berlin Dermatological Society, he was a corresponding member of the French Dermatological Society. He also was a member of the Detroit Dermatological Society and was elected an honorary member of both the Minnesota Dermatological Society and the Society for Investigative Dermatology. In 1946 and again in 1947 he was invited to deliver a series of lectures on dermatologic subjects and histopathology before the staff of the Division of Dermatology at the University of Minnesota. On each occasion he gave freely from his great store of knowledge and endeared himself to all who came in contact with him.

He enjoyed a good cigar and a bottle of rare Rhine wine, and to visit with him after a good meal was like attending a performance of David Warfield in "The Return of Peter Grimm." Here was a man who had known Virchow, Koch and many others whose names are almost legendary, but he could also discuss the virtues and contributions of more recent eminent men, such as Darier, Jadassohn and Arndt. He particularly admired Ehrlich, whom he considered to be the only real genius he had known. His connection with Ehrlich was intimate, both scientifically and personally. Ehrlich married Pinkus' cousin, Hedwig Pinkus. A biography based on his personal knowledge and on Ehrlich's diaries and notebooks was the task of his last two years. It is a pity that death interfered with this work for the interest of all dermatologists in the biography of the inventor of arsphenamine, especially when written by Felix Pinkus, would have been great.

We who knew Dr. Pinkus well regarded him with admiration and sincere affection. He had all the qualities of a great human being. To have had the privilege of learning from him should inspire students to continued search for the explanation of many obscure dermatologic problems. His lectures were erudite and original, for he so often said, "I record only what I myself have seen, not what I have been told." His histologic sketches and his lecture notes constitute another great work well begun, but ended all too soon.

HENRY E. MICHELSON, M. D.

Dedication

This issue is dedicated to Dr. George Miller MacKee, who on June 30, 1947, retired as Director of the Department of Dermatology and Syphilology of the New York Skin and Cancer Unit and the New York Post-Graduate Medical School and Hospital. Doctor MacKee has given liberally of his time, effort and wisdom to American dermatologic periodicals. From 1909 to 1918, he was editor of the *Journal of Cutaneous Diseases, Including Syphilis* and from 1918 to the present time has been a member of the Editorial Board of the ARCHIVES.

The contributors to this volume are former associates, assistants and students of Dr. MacKee, and it is unfortunate that more space is not available in this issue so that other colleagues could also have demonstrated their respect and loyalty by contributing to it. The pleasant task of collecting the material was done by his successor, Dr. Marion B. Sulzberger.

We thank Dr. MacKee for his wholehearted and generous cooperation during the many years he has served as one of the members of the editorial board.

EDITORIAL BOARD.

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TRIBUTE TO DR GEORGE MILLER MacKEE

From His Pupils, Associates and Friends of the New York Skin and Cancer Unit

MARION B SULZBERGER, M D
NEW YORK

ONLY a very small number of the over one thousand pupils and associates of George MacKee have been able to show their appreciation and affection by a contribution to this honor volume of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. I appreciate the opportunity to express, as best I can, the esteem and gratitude of the hundreds of friends and disciples who through the years have profited by MacKee's teaching and example.

No one who worked with or under MacKee has failed to become a better dermatologist, a better physician or a better human being because of his contacts with the Chief. Despite the fact that some have held him to be "a hard man to know," his great qualities as teacher and leader have touched and transmuted each and every one of us.

It is not easy to select from among MacKee's many great qualities those which should be mentioned in this short tribute, but I think that the following selection includes those qualities which all of us would agree are characteristic.

MacKee has always been fair, unprejudiced and impartial. No consideration of origin, of race, of belief, of sex or of social or economic position has ever influenced him one whit in his attitude toward or treatment of his co-workers. All who were willing to give honest service have ever been welcome to the Chief and to his department. The constitution of the present staff of the Department of Dermatology and Syphilology of the New York Skin and Cancer Unit and the Post-Graduate Medical School of the New York University-Bellevue Medical Center attests to MacKee's true democratic spirit in practice as well as theory.

MacKee has ever been modest and faithful. On no occasion has he been willing to take sole credit for his accomplishments. He has always insisted that his fellow workers were those who deserved the major honors. Time after time, at our annual staff dinners and elsewhere, MacKee has told us of his group of staunch friends, of Dave Satenstein, of Fred Wise and Isadore (Ike) Rosen, Bill Abramowitz, Maxie Scheer, Katherine Sullivan and Stella Perkins, and many others, and his voice has inevitably become choked with emotion as he described what he felt

he owed to these co-workers and companions. Each and every man and woman of MacKee's staff and student body knew that beyond any doubt the Chief could be counted on and that he would back them to the limit, whatever their scrapes or troubles.

MacKee has never failed in wisdom or equanimity. In all my nineteen years of association with him, I have on every occasion gained something of value from his advice—whether on medical matters, on personal affairs or on other and wider problems. Trying as we younger folk often must have been, selfish and inconsiderate in adding some petty personal burden to the Chief's heavy load, none of us has ever found MacKee angry, impatient or inconsiderate. He seemed to be able to draw on a limitless store of patience and understanding. To come into his presence in his small unpretentious office, with its walls covered with the pictures of the dermatologic great, was always like coming out of the din and clangor of turbulent battle into a quiet and shaded place, full of comfort and strength.

This is a woefully incomplete account of how we, his pupils and associates, feel about George MacKee, but I hope that it may serve to show in some measure why MacKee has been so successful in building and organizing a great teaching and research institute in American dermatology.

By nature's endowments and through the school of rigid self discipline, MacKee is a chief in every true sense of the word—a man to be relied on, to be followed and to be loved by those who know him.

GEORGE MILLER MacKEE, M D , AN OUTSTANDING DERMATOLOGIST AND LOYAL FRIEND

HOWARD FOX, M D
NEW YORK

I FELT highly flattered on being asked to write the story of Dr. MacKee's accomplishments to honor him in this issue of the ARCHIVES. I first met George MacKee in Fordyce's Clinic at the New York University in 1906, shortly after the appearance of his article on staining of the *Spirochaeta pallida*¹. I wanted some information on the subject, and McKee gave it willingly. This was the beginning of an unbroken close friendship for over forty years. Although he was a young man beginning to learn dermatology, as I was, I was greatly impressed by the serious interest in his work and prophesied that he would eventually become a great leader in our specialty. He made the same impression on Dr. George T. Jackson and others, including my father. Needless to say, my prophesy came true.

Dr. MacKee is a perfect example of a self-made man, as he said "self educated and to a large extent self trained". He was born in 1878 in Jersey City, N. J., of American parents of Scotch, Irish, Dutch and French ancestry, and moved to Stamford, Conn., at the age of 2. His early training consisted of a grammar school education, one winter in a business school and three years as a medical student in the New York University (then called New York University and Bellevue Hospital Medical College). In his school years, he worked as a bicycle and printer's mechanic, from the age of 13 to 17. He became a splendid athlete and helped himself through medical school by giving athletic instruction, playing professional basket ball and acting as a deep sea fisherman and beach guard at Ocean Grove, N. J., during the summer vacations. For several years after graduation, it was necessary for him to engage in professional athletics and to practice general roentgenologic work and physical therapy. He joined Dr. Fordyce's Clinic at the New York University in 1903.

George MacKee was the type who would have made his mark as either a professional or business man. The secret of his great success was his ambition and extraordinary capacity for work. He was a serious, kindly man who treated his assistants well. He had their whole-

¹ MacKee, G. M. The *Spirochaeta Pallida* in Syphilis, with Special Reference to Goldhorn's Rapid Staining Method, New York M. J. 83:588, 1906.

hearted support, which was shown when he resigned from the College of Physicians and Surgeons and was offered the professorship of the Department of Dermatology at the New York Post-Graduate Medical School and Hospital. Approximately twenty-eight of his assistants resigned with him and helped later to build up the largest dermatologic clinic in the world.

The first piece of great fortune which befell MacKee was when Dr. Fordyce made him his chief of clinic at Columbia, after he had left the New York University. As Fred Wise said in his delightful sketch, MacKee "never stood in need of incentive or stimulus from anybody, but it was Fordyce who inspired him and encouraged him."² One of the greatest kindnesses shown by his chief to MacKee was making him editor of the *Journal of Cutaneous Diseases, Including Syphilis*. He held this position from 1909 to 1918. While it proved a difficult job, it was a liberal education for MacKee, who took the work as seriously as anything in his career. It was a great help to him in writing excellent English and in learning dermatologic terminology.

Dr. MacKee dedicated the first volume of his book on roentgen rays to Dr. Fordyce and after his death wrote a beautiful tribute to him in the ARCHIVES.³ Dr. MacKee's editorial experience made him a valuable member of the editorial board of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY since 1918, the *Journal for Investigative Dermatology* since 1939 and *Dermatology and Venereology* since 1946.

OUTSTANDING ACCOMPLISHMENTS

The Historian's files of the American Dermatological Association contain so much material about George MacKee that I thought it best to ask him what he considered his most important accomplishments. He described, in modest terms, two items that had given him the greatest satisfaction, one was his book on roentgen rays, and the other was the formation of a self-contained dermatologic department. He added the statement, with which I cannot agree, that these were "the only two of any importance."

Dr. MacKee's greatest achievement was undoubtedly the publication of his book on "X-Rays and Radium in the Treatment of Diseases of the Skin."⁴ The basic knowledge needed to write this invaluable book, now in its fourth edition, was his early experience in practice. As he said, he practiced deep and superficial roentgen therapy, radium

² Wise, F. Dr. George Miller MacKee, *J. Invest. Dermat.* 8:277 (June) 1947.

³ MacKee, G. M. John Addison Fordyce, *Obituary*, *Arch. Dermat. & Syph.* 12:268 (Aug.) 1925.

⁴ MacKee, G. M. *X-Rays and Radium in the Treatment of Diseases of the Skin*, Philadelphia, Lea & Febiger, 1921.

therapy and physical therapy while endeavoring to become a dermatologist. Probably his comprehensive knowledge of all these subjects is unique among dermatologists. In his writing on the "Arithmetical Computation of Roentgen Dosage,"⁵ he had the valuable assistance of Dr. John Remer, who was an excellent mathematician.

Dr. MacKee wrote me that he believed that his "x-ray book, especially the first two editions, was of practical value to dermatology." This was modesty personified for a book that revolutionized the treatment of skin diseases with roentgen rays. It was published at a time when therapeutic resourcefulness in our specialty was considerably less than at present. The technic is eminently safe, as has been found by the successful treatment of thousands of cases of ringworm of the scalp. MacKee also suggested that his early work in physical therapy kept cutaneous physical therapy in dermatology instead of in physical medicine.

In 1915, I had to attend a meeting of the American Medical Association in San Francisco and persuaded George to go with me. The trip was an eye opener for him as he had never previously traveled any distance. We went by way of the Canadian Rockies and spent a week in the Glacier National Park on the way home. While crossing the Bad Lands of South Dakota, George became disgusted with the trip. However, as we approached Banff, he came to life with a vengeance and soon became enamored of the beautiful mountain scenery. On this trip we did some traveling by horseback, which gave George a chance to exhibit his great talent as a photographer. The trip pleased him so much that for a number of years he spent his vacations in the Canadian Rockies, where he became a splendid mountain climber. He was later made a member of the Canadian and of the American Alpine clubs.

One of the few occasions on which I have seen George become greatly excited occurred at 7 a. m. in our hotel room in Glacier Park. He woke me up with a shout, which made me think that at least a grizzly bear was about to enter our room. I rushed to the window and was delighted to see a beautiful reflection of the mountains in the lake, which we both photographed, and we admitted that it was difficult to tell which were the mountains in the distance and which was the reflection.

Because of overwork in writing the first edition of his book on roentgen rays and spending his vacations in strenuous mountain climbing, MacKee unfortunately contracted pulmonary tuberculosis, which kept him out of work for five years. Fortunately, his prac-

⁵ MacKee, G. M. *Arithmetical Computation of Roentgen Dosage*, J. Cutan. Dis. 37:783 (Dec.) 1919.

tice was kept up by Dr Earl D Crutchfield (deceased), Dr. Lawrence K McCafferty (deceased), Dr M J Gibans, Dr Blanche Norton, Dr Clarence H Peachey, Dr Chris Halloran and especially Dr George C Andrews, who was in charge for several years. Invaluable help was given by his faithful and efficient secretary, Miss Katherine M Sullivan. As I had originally recommended Miss Sullivan to MacKee, I did not feel too guilty about introducing him to mountain climbing in the Canadian Rockies.

The second important achievement in MacKee's opinion was the formation of a self-contained dermatologic department, beginning in Fordyce's Clinic and continuing when the Skin and Cancer Hospital was combined with the New York Post-Graduate Medical School and Hospital. This made it possible to obtain satisfactory full time graduate training in dermatology without going to Europe, and almost without going out of the department. It is hardly necessary to say that when the two institutions were united, the dermatologic clinic became the largest in the world, with a staff of one hundred and seventeen dermatologists, and, of course, one of the most famous. MacKee made the following important comment: "Such self-contained departments throughout the United States, with basic medical science research, have helped to prevent dermatology from being absorbed by medical departments." MacKee also told me that approximately seven hundred physicians had obtained their training in dermatology in his organization. For the success of his department, MacKee insists on giving full credit to his large, loyal and capable staff, especially to his well known key men, Fred Wise, Isadore Rosen, Elias W Abramowitz, David L Satenstein and Max Scheer, and, during the last fifteen years, to his efficient departmental secretary, Miss Stella Perkins.

Dr MacKee has had some academic title in a medical school during most of his professional life, having served in the New York University, Columbia University and the New York Post-Graduate Medical School. Probably the greatest academic honor he received was his recent appointment as professor emeritus of clinical dermatology by Columbia University. This honor came after the separation of Columbia University and the Post-Graduate Medical School. It is also the first occasion for a member of an affiliated institution to receive an emeritus degree from Columbia.

In Fordyce's Clinic at the New York University, Dr MacKee was instructor in dermatology and syphilology, and in the same clinic at the College of Physicians and Surgeons, he served successively as instructor (1910-1918), assistant professor (1918-1926) and professor of dermatology and syphilology (1926-1933).

At the New York Post-Graduate Medical School, MacKee became professor of clinical dermatology and syphilology and executive officer

of the department, including the Skin and Cancer Hospital, the name of which was changed to the Skin and Cancer Unit of the New York Post Graduate Medical School and Hospital. Other academic appointments included lecturer on dermatology and syphilology at the Trudeau School of Tuberculosis (1927-1933), lecturer at the Angle School of Orthodontia (1906-1912) and lecturer on dermatology and syphilology in the Fone's School for Dental Prophylactic Technicians (1913-1917)

SOCIETY MEMBERSHIPS

In local societies Dr MacKee is an active member and past president of the New York Dermatological Society, an honorary member and past president of the Manhattan Dermatological Society, honorary member of the Brooklyn Dermatological Society, president (1941) of the Association of Dermato-syphilologists of Greater New York, past chairman of the Section of Dermatology and Syphilology of the New York Academy of Medicine (1917), charter member and past president of the New York Roentgen Society and past president of the Alumni Federation of the New York University

The most important national society to which MacKee belongs is the American Dermatological Association, of which he was president in 1926 and treasurer from 1930 to 1947. He became a member in 1911 and recently resigned to become a senior inactive member. In the American Medical Association, he was a charter member of the Council on Physical Therapy, resigning in 1940. He was also chairman of the Section on Dermatology and Syphilology in 1932. He was chairman of the Section on Dermatology and Syphilology of the Medical Society of the State of New York in 1934. He was president of the American Academy of Dermatology and Syphilology in 1941 and a charter member of the American Board of Dermatology and Syphilology, resigning in 1938. He was president of the Society for Investigative Dermatology in 1937. He is an active member of the American Roentgen Ray Society, the American Radium Society and a fellow of the American College of Radiology. He has been an honorary member of the Stamford (Conn.) Medical Society since 1946, and was formerly a member of the American Urological Association (1904-1910).

Dr MacKee has received abundant recognition from foreign countries for his scientific publications. He is a corresponding member of the Argentine, British and Hungarian Dermatological Societies and an honorary member of the Cuban, French and Japanese Dermatological Associations, the London Dermatological Society, St John's Hospital Dermatological Society of London, the Wiener Dermatologische Gesellschaft, the Radiological Society of North America and the Venezuelan Society of Dermatology and Venereology (1948).

HOSPITAL APPOINTMENTS

Dr MacKee's appointments were made in the following hospitals St Vincent's, as roentgenologist (1905-1910) and consulting dermatologist (1910 to date), Presbyterian, as assistant attending dermatologist (1910-1926), New York Post-Graduate (1926-1947), Reconstruction Unit, as attending dermatologist and syphilologist (1926-1947), Welfare, First Division, as attending dermatologist (1939-1944) He is now consulting dermatologist to Passaic General Hospital (since 1905), Stamford Hospital (since 1905), Port Chester Hospital (since 1905), Yonkers Hospital (since 1906), St Lukes Hospital (since 1932), Holy Name Hospital, Teaneck, N J (since 1939) and St Joseph's Hospital, Stamford, Conn (since 1946) He was formerly consulting dermatologist to Sea View Hospital (1915-1934)

TRIBUTE

Two recent events meant a good deal to MacKee One was a surprise dinner given in 1939 to celebrate his forty years in medicine He was presented with a bound volume, of which there is only one copy, containing photographs and tributes from each of his thirty-three office assistants Dr Wilham H Guy was largely responsible for this honor paid to his former chief The other event, at which I had the pleasure to be present, was the annual staff dinner on March 16, 1946 It was a farewell tribute to Drs MacKee, Wise and Rosen, on which occasion each was presented with a handsome gold watch by the staff Both Wise and Rosen were retiring according to custom at the age of 65 MacKee was urged to continue but was willing to serve only one more year

It is obvious from this brief sketch that George MacKee has fulfilled my prophesy of becoming a great leader in dermatology He has held almost every possible dermatologic honor and merits his retirement from active practice, which he recently announced He realizes that a large number of honorary positions chiefly add to his reputation He also knows, as I do, the definition of a hospital consultant, namely, one who is rarely called in for consultation

We have traveled together twice to California, once to Mexico and many shorter distances We have served together for years in various dermatologic societies While disagreeing on a few minor questions, we have remained close friends for over forty years His advice to me about roentgen rays in my early years was invaluable My advice to him was not to work too hard

I have long admired George for his courage, honesty, kindness and fairness to his associates, his administrative ability and his extraordinary capacity for work He is a perfect example of a most successful self-made man and a loyal friend I have never known another

man who could work as hard and accomplish as much as George MacKee has since his illness. As he is five years younger than I am, I expect that he will outlive me. In his delightful home on the outskirts of Stamford, Conn., I wish him all possible good fortune in the coming years.

140 East Fifty-Fourth Street (22)

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TREATMENT OF BASAL CELL EPITHELIOMA BY INJECTION OF TISSUE EXTRACTS

A Further Report

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CINCINNATI

IN A PREVIOUS report¹ the results of treatment of basal cell epitheliomas with tissue extracts prepared from human spleen and liver were described. The small number of normal human organs available for this work limited the number of patients who could be accepted for treatment. Obviously, the immediate problem resolved itself into the location of more plentiful sources of the effective principle.

In the laboratory constant emphasis has been placed on the problem of determining the nature of the principle. It is hoped that a more thorough understanding of its nature will be helpful in eventually pointing the way toward synthesis, as has been the case with some of the vitamins. Our more immediate approach, however, has been of the "cut and try" type, a testing of extracts of organs which were readily available.

Fardon, Brotzge and Loeffler,² for example, in working with heterologous tissue extracts, demonstrated that rabbit spleen pulp is effective in increasing resistance to transplantable mouse carcinoma 15091a, and, likewise, a deproteinized beef spleen extract showed some power to induce resistance to the same mouse carcinoma. However, they concluded that these extracts "failed to induce a resistant state comparable to that elicited by the homologous tissue pulps and extracts."

This research was made possible partly through a grant from the Lillia Babbitt Hyde Foundation.

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University, and the Institutum Divi Thomae, Cincinnati.

1 Amersbach, J. C., Walter, E. M., and Sperti, G. S. Treatment of Basal Cell Epithelioma by Injection of Tissue Extracts. A Preliminary Report, *Arch. Derm. & Syph.* **54** 119-132 (Aug.) 1946.

2 Fardon, J. C., Brotzge, G. C., and Loeffler, M. K. The Role of Homologous and Heterologous Tissue Extracts in the Establishment of the Resistant State Against Carcinoma, *Stud. Inst. Divi Thomae* **3** 69-80, 1941.

Lewisohn³ had also found a beef spleen extract to cause regression of mouse sarcoma 180

From these results it seemed likely that extracts of heterologous tissues, such as those of beef spleen and lamb liver, might prove effective in the treatment of human cancer, even though they might be less effective than homologous tissue extracts

THE PREPARATION OF SPLEEN AND LIVER EXTRACTS

Beef spleens and lamb livers were obtained from freshly slaughtered animals. The extracts were prepared by the same procedure used for the extracts of human tissues

The liver and the spleen extracts were prepared separately. The tissues were weighed, trimmed of all fat and extraneous connective tissue, ground thoroughly and then added to a volume of distilled water corresponding to the weight of the tissue, i. e., 100 cc of water per hundred grams of spleen. The suspension was frozen and thawed three times, one day being allowed for each freezing and thawing procedure. The proteins were then precipitated by adding increasing concentrations of 95 per cent alcohol to the *brev.* First, alcohol was added to a final concentration of 50 per cent, and the mixture was allowed to stand for two hours. Finally, the concentration was raised to 80 per cent, and the mixture was allowed to stand for one day and then filtered free of tissue and precipitated protein. The extract was concentrated *in vacuo* approximately to the volume of distilled water added originally. This water solution was then extracted with three separate portions of ether of a total volume equal to that of the water solution. The ether solution was discarded, and the water solution was evaporated almost to dryness. The residue was made up to the desired concentration with distilled water.

A concentration of tissue extract equivalent to .15 Gm of tissue was used. The p_H of the extract was adjusted to 6.5 to 7 with potassium hydroxide, and the extract was boiled for thirty minutes. After standing in the refrigerator overnight the solution was filtered. The extract was then put in serum bottles and was boiled for thirty minutes on each of three successive days. Each sample of extract prepared was tested for toxicity by injecting into a guinea pig the same amount to be used subsequently on a patient. Ill effects were not shown either by the animals or by the patients.

CLINICAL PROCEDURE

The clinical procedure was the same as that employed with the human extracts reported in the previous paper¹. Patients with small

³ Lewisohn, R. Effect of Subcutaneous Injections of Concentrated Spleen Extract on Mouse Sarcoma 180, Surg, Gynec & Obst. 66 563-576, 1938

basal cell epitheliomas varying from pea size to 3 or 4 cm across in the longest dimension were selected indiscriminately as they appeared in the clinic service. Before any treatment was given, a colored photograph

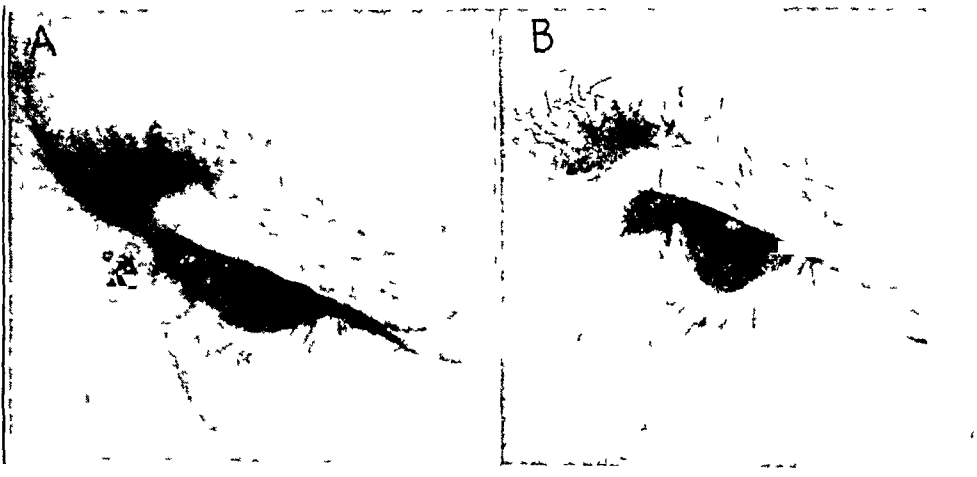


Fig 1 (case 31)—*A*, basal cell epithelioma on the left inner canthus before treatment, *B*, after twenty-three injections of beef spleen

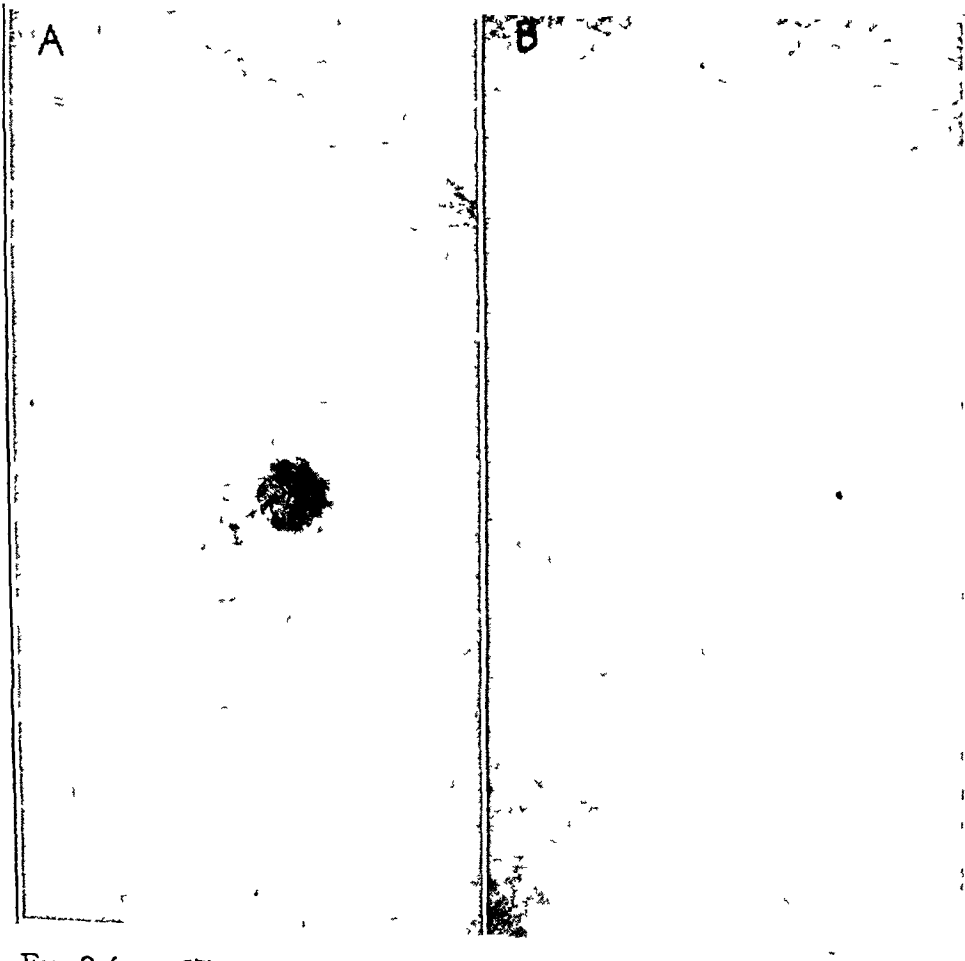


Fig 2 (case 37)—*A*, intraepidermic basal cell epithelioma on the scalp before treatment, *B*, after nine injections of beef spleen

Case Histories of Patients Treated with Tissue Extracts

Case	Patient	Sex	Age	Location and Description of Lesion	Pathologic Report	Treatment	Duration of Treatment	Result
22	I N	M	40	Pea sized lesion with raised borders on tip of nose	Infiltrating basal cell epithelioma	Human spleen, 7 injections	3/15/44 to 7/19/44	Complete regression
23	V S	F	70	Large pea sized nodular lesion on inner canthus of upper right eyelid	Basal cell epithelioma	Human spleen, 23 injections	5/24/44 to 10/23/45	Failed to regress
24	B G	M	33	Large pea sized eroded area with pearly borders on right cheek	Basal cell epithelioma	Human spleen, 20 injections	5/31/44 to 4/4/45	Complete regression
25	G B	M	69	Dime-sized lesion with central ulceration and pearly borders under left lower eyelid (report of anaplastic during treatment)	Basal cell epithelioma	Human liver, 10 injections	6/12/44 to 1/22/45	Complete regression
26	B W	M	55	Nickel sized lesion with rolled pearly borders on right preauricular area	Basal cell epithelioma	Human liver, 34 injections	6/14/44 to 4/23/45	Complete regression
27	I K	M	33	Large ulcerated lesion 2 by 3 cm on left side of cheek	Recurrent basal cell epithelioma	Human liver, 11 injections	9/13/44 to 1/15/45	90% regression, patient failed to continue treatment
28	O F	F	39	Quarter sized raised lesion with central ulceration and pearly borders on right cheek, recurrence of previous surgical excision	Basal cell epithelioma	Human liver, 38 injections, beef spleen, 7 injections	10/4/44 to 1/3/46	Complete regression
29	H S	M	73	Large pea sized lesion with central ulceration and pearly borders on right cheek	Basal cell epithelioma	Beef spleen 26 injections	1/10/45 to 4/3/46	Complete regression
30	E R	M	62	Lesion 1.27 by 3.81 cm with central ulceration and pearly borders on left preauricular area	Basal squamous cell epithelioma	Beef spleen, 16 injections	1/10/45 to 6/9/45	Regression slow, lesion excised
31	C M	M	67	Pea sized lesion with central ulceration and pearly borders on left inner canthus	Basal cell epithelioma	Beef spleen 22 injections	1/17/45 to 7/11/45	Complete regression
32	M S	F	36	Small pea sized raised pearly lesion on right side of nose	Basal cell epithelioma	Beef spleen, 11 injections	1/17/45 to 5/16/45	Complete regression

JJ	D L	F	47	Dime sized lesion previously treated with electric needle on right temple	Basal cell epithelioma	Beef spleen, 10 injections	2/21/45 to 8/22/45	Complete regression
34	A F	F	62	Dime sized raised lesion on right cheek	Senile keratosis	Beef spleen, 10 injections	4/18/45 to 10/8/45	90% regression, patient failed to continue treatment
35	O L	M	51	Raised pea sized pearly lesion on right side of nose	Basal cell epithelioma	Beef spleen 10 injections	5/2/45 to 11/11/45	Complete regression
36	C F	F	40	Dime sized raised pearly lesion with central ulceration on forehead	Infiltrating basal cell epithelioma	Beef spleen, 8 injections	6/18/45 to 11/19/45	Complete regression
37	C O	M	82	Quarter sized raised black crusted lesion on scalp	Intraepidermic basal cell epithelioma	Beef spleen, 9 injections	6/18/45 to 10/29/45	Complete regression
38	O R	M	45	Large pea sized pearly raised lesion under right eye	Basal cell epithelioma	Beef spleen, 8 injections	7/9/45 to 11/26/45	Complete regression
39	M D	M	70	Raised superficial lesion 1.27 cm in diameter on right temple	Basal cell epithelioma	Lamb liver, 13 injections	7/30/45 to 5/6/46	90% regression, still under treatment
				Red lesion 1.27 cm in diameter, 0.64 cm raised with central ulceration on back of neck	Basal squamous cell epithelioma	Lamb liver, 15 injections	7/30/45 to 5/6/46	Complete regression
40	I S	F	69	Pea sized ulcerated lesion on bridge of nose	Prickle cell epithelioma	Lamb liver, 6 injections	9/12/45 to 11/28/45	Complete regression
41	R O	M	39	Pea sized ulcerated lesion with pearly borders on left nasolabial fold	Basal cell epithelioma	Lamb liver, 13 injections	10/23/45 to 5/29/46	70% regression, still under treatment
42	B S	F	62	Quarter sized lesion with central ulceration and pearly borders on left temple	Basal cell epithelioma	Lamb liver, 18 injections	10/23/45 to 5/29/46	70% regression, still under treatment
43	J B	M		Dime sized raised pearly lesion on center of forehead	Basal cell epithelioma	Beef spleen 16 injections	11/11/45 to 4/17/46	70% regression, still under treatment
44	M W	M	48	Pea sized lesion with central ulceration and pearly borders on lower eyelid near left inner canthus	Basal cell epithelioma	Lamb liver, 19 injections	11/7/45 to 5/1/46	90% regression, still under treatment
45	E M	F	80	Large raised nodular lesion 5.08 by 3.81 cm and 1.27 cm raised with central ulceration on right temple	Infiltrating anaplastic epithelioma	Beef spleen, 9 injections	1/1/46 to 6/3/46	Somewhat improved, still under treatment

* The preceding 21 case histories are tabulated in the preliminary reports ¹

was taken of the lesion, and a biopsy was performed for pathologic diagnosis of the lesion. The patient was then given a series of weekly intradermal injections varying from 0.25 to 2.5 cc of the extract. At each treatment the lesion was infiltrated, until the lesion and the surrounding tissue for about $\frac{1}{4}$ inch (0.64 cm) became blanched and hard. After the lesion had regressed clinically a post-treatment biopsy was taken to determine whether any malignancy remained.



Fig 3 (case 39)—*A*, spinobasal cell epithelioma on the back of the neck before treatment, *B*, after fourteen injections of lamb liver

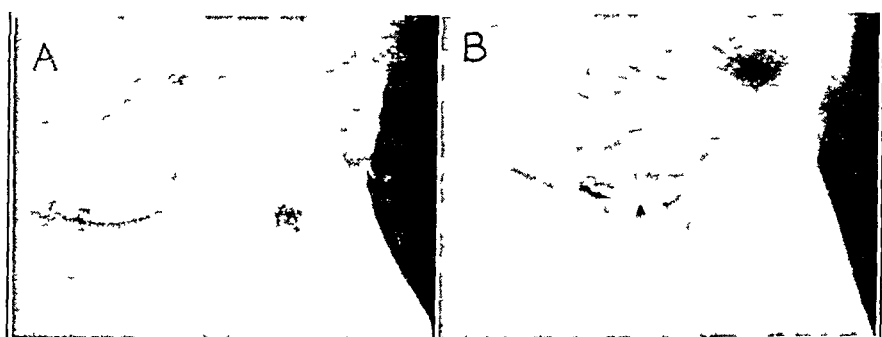


Fig 4 (case 40)—*A*, prickle cell epithelioma on the bridge of the nose before treatment, *B*, after six injections of lamb liver

RESULTS

Results are reported for 24 patients, of whom 3 were treated with human spleen extract, 3 with human liver extract, 12 with beef spleen extract, 5 with lamb liver extract, and 1 with both human liver and beef spleen extract. Actually, six lesions were treated with lamb liver extract, since 1 patient had two lesions. The case histories are given in the accompanying table, and photographs of several patients before and after treatment are shown.

It may be well to summarize the 45 cases reported in the previous and in the present paper. In the seventeen lesions treated with human spleen extract there were eleven complete regressions, two slow regres-

sions in which the lesion was excised, two which had regressed 50 per cent and 80 per cent respectively when last seen, and two failures. In the ten lesions treated with human liver extract, there were seven complete regressions, one slow regression in which the lesion was excised and two which had regressed 90 per cent when last seen. In the 12 cases in which treatment was with beef spleen extract, there were eight complete regressions, one slow regression in which the lesion was excised, one with 90 per cent regression when last seen and two still under treatment showing definite regression. In the case in which treatment was with both human liver extract and beef spleen extract, there has been complete regression. In the 5 cases with six lesions treated with lamb liver extract there were three complete regressions and three lesions still under treatment which showed 70 to 90 per cent regression.

It will be noted that the present series of lesions includes a spinobasal cell epithelioma and a prickle cell epithelioma. These more malignant epitheliomas likewise regressed completely when treated with the tissue extract.

SUMMARY

Of the forty-six lesions reported in this and in the preceding paper, two failed to respond, four were excised because of slow regression, five showed 50 to 90 per cent regression when last seen, five were still under treatment at the time of writing but had shown definite regression, and thirty showed complete regression.

NOTE.—In the previous publication¹ references to the work by Albert Braunstein on the use of spleen therapy in the treatment of experimental animals and in 2 cases of human external cancer were unintentionally omitted.

Braunstein, A. The Problem of the Prophylaxis of Cancer from the Immunobiological Standpoint, *M. Woman's J.* **51** 25-32, 1944, Ueber die Bedeutung der Milz in der Geschwulst-Immunität und Therapie (Ein neues Verfahren der Krebsbehandlung) I. Experimenteller Teil, *Berl. klin. Wchnschr.* **48**:2029-2031, 1911.

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CONTACT ROENTGEN THERAPY

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IT WAS twelve years ago that I first saw the Chaoul contact therapy apparatus¹ used by Prof Woodburn Morrison at the Cancer Hospital in London, and since then I have been interested in this subject. There are only a few Chaoul machines in the United States, which were imported from Germany prior to the war. Here the Philips contact therapy apparatus is more widely used. Therefore my paper will be mostly about the Philips machine. I will speak as a clinician of its merits and shortcomings.

At the risk of repetition I will briefly describe the construction of contact therapy tubes. In the Chaoul type of tube the short target-skin distance is made feasible by mounting a gold-plated nickel target at the extreme end of the tube, where it serves not only as a target but also as a filter, because the beam of roentgen rays passes through it. This filtration produces a rather strongly filtered beam. In the Philips tube, the filament is the grounded electrode near the end of the tube and the target is set back a short distance. The roentgen ray beam in the Philips tube does not pass through the target but only through a thin glass window and a cap of plastic material which has a filtration equivalent to 0.2 mm of aluminum. When the face of the tube is in contact with the skin, the target-skin distance is 18 mm. This distance may be slightly increased by the use of cones, so that target-skin distances of the order of 2 and 4 cm are in everyday use.

The physical factors of low voltage contact roentgen therapy have been described by Quimby,² Braestrup³ and others. Maynard⁴ observed that the ray quality of the Chaoul tube is equivalent to a half-value

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 4, 1946.

1 Chaoul, H. Die Behandlung Bosartiger Geschwulste durch eine der Radiumtherapie angepasste Röntgenbestrahlung, München med Wchnschr, **81** 235-239, 1934.

2 Glasser, O., Quimby, E. H., Taylor, L. S., and Weatherwax, J. L. Physical Foundations of Radiology, New York, Paul B. Hoeber, Inc., 1944.

3 Braestrup, C. B., and Blatz, I. H. Physical Factors in Low Voltage "Contact" Roentgen Therapy, Radiology **35** 198-205, 1940.

4 Maynard, W. V. Measurements of Low Voltage X-Rays, Brit J Radiol **9** 215-238, 1936.

layer of 3.3 mm of aluminum, and Quimby⁵ wrote that this is considerably harder than the radiation obtained with standard superficial therapy apparatus in common use in this country, which produces radiation with a half-value layer of about 1 mm of aluminum when operated at 100 kilovolts without a filter. She concluded that any advantage in the Chaoul equipment lies not in the quality of the radiation but in the shape of the tube, which permits its insertion into the body cavities, and in the short distances that can be used.

However, the shape of the tube is no longer a special advantage, because with modern shock-proof equipment and intracavitary visual cones one can treat lesions in the mouth and other body orifices even more readily and more accurately than is possible with contact therapy tubes. Therefore, the chief advantage of the Chaoul tube is its short target-skin distance, and the same statement may be applied to the Philips tube.

COMPARISON WITH RADIUM APPLICATORS

In regard to the quality of the radiation from the Philips tube, one must keep in mind that, although it is loosely compared to that produced by radium applicators, it is different. The radiation from the Philips tube, as already mentioned, is of a soft quality, and even when passed through a filter of 2.5 mm of aluminum the half-value layer, according to Quimby, is only 1.6 mm of aluminum. In the treatment of cutaneous diseases, radium plaques so softly filtered are not generally used but a filter of 0.5 mm of platinum or 2 mm of brass is applied. This cuts out all the beta rays and allows 100 per cent gamma radiation. This radiation has a half-value layer of about 1.2 cm of lead.

CHART 1 Braestrup has compared the depth doses of contact roentgen therapy with those obtainable with radium. He stated that a radium tube 20 mm long with 0.5 mm of platinum filtration applied at 7 mm distance from the skin will give the same proportionate depth dose at 1 cm below the surface as the Philips contact therapy tube operating at 44 kilovolts unfiltered. This seeming similarity is due largely, as Braestrup has explained, to the factors of distance rather than to any similarity in the quality of radiation.

CHART 2 With Dr. Quimby's permission I am including a chart from her article which shows the curves of depth dosage with the Philips contact therapy tube and with a radium plaque at a distance of 2 cm. By placing the radium at a distance of 2 cm instead of 1 cm and by using a plaque instead of a tube the whole analogy is changed. From this chart one can readily see that there is no similarity between the quality of unfiltered radiation with a Philips tube and that of the

⁵ Quimby, E. H., and Focht, E. F. Dosage Measurements in Contact Roentgen Therapy, *Am J Roentgenol* 50:653-668, 1943.

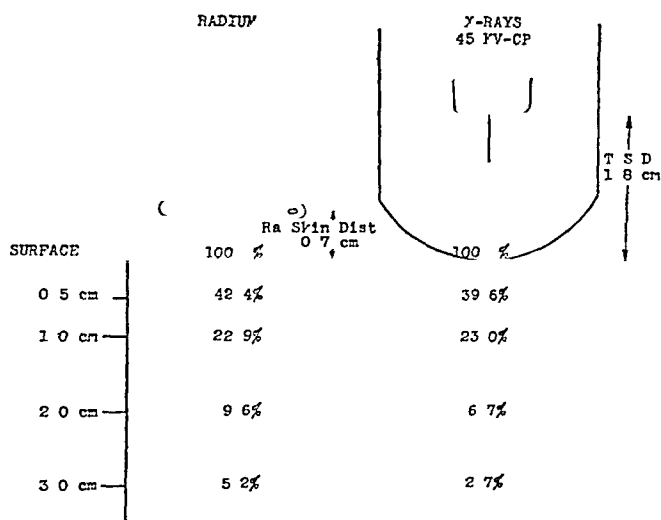


Fig 1—Comparison of depth doses of contact roentgen therapy with those obtainable with radium (Courtesy of Dr C B Braestrup)

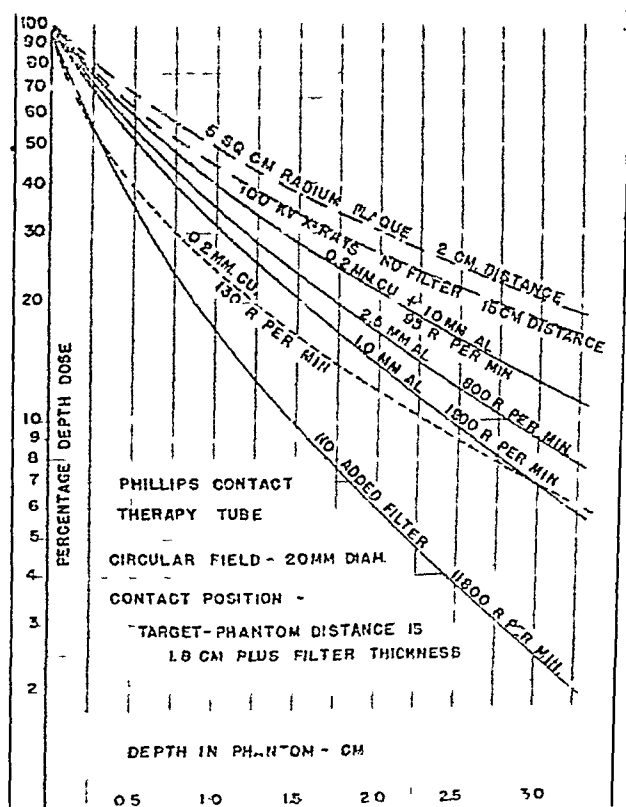


Fig 2—Curves, showing percentage depth doses for unfiltered and filtered 44 kilovolt roentgen rays (Courtesy of Dr E H Qumby and Dr E F Focht)

radium applicator Although the distribution of the radiation within the tissues under conditions mentioned by Dr Braestrup may be similar, the quality of the radiation is entirely different Whether quality of itself influences the biologic effects is a question, but certainly the clinical results are not the same with the Philips tube and the radium applicator

In this connection Braestrup called attention to the differences in the rate of dosage It would be practically impossible to duplicate the high rate of dosage with roentgen rays because it would require 35 Gm of radium to do so In other words, the Philips tube delivers 10,000 to 16,000 r per minute, whereas with ordinary radium applicators screened with 0.5 mm of platinum twenty to forty hours are necessary to produce such a quantity of radiation That the biologic effect is influenced by the rate of dosage is established in a general sense This is well

TABLE 1—*Comparison of Depth Doses of Roentgen Rays and Radium**

Type Kilovolts	Roentgen Rays							Radium
	Grenz 10	Contact 45	Low 65	Voltage 100	Intermediate 135	High Voltage 135	High Voltage 200	Gamma Rays 0.5 1 0 pt
Filter (mm)	0	0	2 alumi num	0	3 alumi num	0.25 cop per +1 aluminum	0.50 cop per +1 aluminum	
Distance	10 cm	1.8 cm	15 cm	15 cm	15 cm	15 cm	50 cm	1 cm
Field diameter	2.5 cm	2.5 cm	2.5 cm	2.5 cm	2.5 cm	2.5 cm	2.5 cm	
0 (surface)	7700	208	111	134	114	109	105	201
0.5 cm	100	100	100	100	100	100	100	100
1.0 cm		48	86	79	89	91	93	60
3.0 cm		5.6	37	32	53	58	67	15
5.0 cm		1.2	17	12	28	37	47	7.0
10.0 cm				2.2		9.2	19	

* From Braestrup and Blatz (Radiology 35: 198-205, 1940)

illustrated by comparing the number of roentgens necessary to produce erythema if given in a single dose with the number necessary if the dose is divided and given over several days The differences in the rates of dosage expressed here are doubtless sufficient to modify noticeably the clinical effect

TABLE 1 In Table 1, Braestrup has compared the depth doses of roentgen rays of various voltages that are commonly used and the gamma rays of radium from a tube at a distance of 1 cm It will be seen that in order to obtain a uniform dose of 100 r at a depth of 0.5 cm it is necessary to vary the surface dose within a wide range extending from 7,700 r for grenz rays to 105 r for high voltage radiation Also one notes in this chart the influence of distance on depth dose for the radiation produced at 200 kilovolts at 50 cm target-skin distance has a much larger depth dose than gamma radiation from a distance of 1 cm This relationship would be completely altered if the radium were placed at a greater distance Roentgen ray apparatus with a capacity

of 1,000,000 volts is required to produce the equivalent of gamma radiation

TABLE 2 The effect of filtration on the distribution of the dose is shown by Braestrup in table 2, using radiation produced by the Philips tube which runs at a constant potential of 45 kilovolts and at 2 milliamperes. As stated, the inherent filtration is equivalent to 0.2 mm of aluminum. Without additional filter a surface dose of 13,000 r gives a dose at a depth of 1 cm of 3,000 r. When a filter of 1 mm of aluminum is added a surface dose of 8,250 r gives a dose at a depth of 1 cm of 3,000 r. When the filtration is increased to 0.2 mm of copper and 1 mm of aluminum the same depth dose at 1 cm can be obtained by giving a surface tissue dose of 6,450 r. In other words, the percentage of depth dose at 1 cm is doubled from 23 per cent to 46 per cent by using a filter of 0.2 mm of copper and 1 mm of aluminum.

TABLE 2—*Effect of Filtration on Dose Distribution**

Voltage	45 kilovolts constant potential		M A 20	
Filter	0.2 mm aluminum	1.2 mm aluminum	0.2 mm copper, 1 mm aluminum	
High voltage	0.28 mm aluminum	1.04 mm aluminum	3.8 mm aluminum	
Distance	1.8 cm	2.1 cm	2.1 cm	
Diameter of field	2.5 cm	2.9 cm	2.9 cm	
(r/min in air)	9,500	1,470	245	
	Tissue Dose (Roentgens)		Tissue Dose (Roentgens)	
Surface	100% 13,000	100% 8,250	100% 6,450	
1 cm	23.0 3,000	36.3 3,000	46.6 3,000	
2 cm	6.7 870	14.4 1,190	24.3 1,560	
3 cm	2.7 350	6.7 553	14.1 905	
5 cm	0.6 78	1.9 157	5.6 354	
Time	1'20"		5'18"	
			24'36"	

* From Braestrup and Blatz (Radiology 35: 198-205, 1940).

TREATMENT OF EPITHELIOMAS

The results in the treatment of epitheliomas with the Philips tube are no better and often are not as good as those obtained with standard superficial therapy machines with unfiltered radiation produced at 60 or 100 kilovolts. The advantage of the Philips tube lies in the protection of deeper structures and the rapidity with which large doses can be given.

With the Philips apparatus I use 8,000 r to 16,000 r, unfiltered except for the filtration inherent in the tube. This is given in divided doses in eight to twelve exposures over a period of two to three weeks. The size of the dose is changed according to the thickness, or depth, and size of the epithelioma, the amount of subcutaneous tissue, the proximity of bone or cartilage and the patient's age and type of skin. These large doses cause severe reactions, which, however, are superficial and heal with surprisingly little scarring.

My impression is that I get just as good clinical results in the treatment of small superficial epitheliomas with 6,000 r to 8,000 r in divided dosage at 60 to 100 kilovolts as I get with 10,000 r to 16,000 r in divided dosage with the Philips tube. However, many epitheliomas are larger than the area that the Philips tube covers. The end of the tube is circular and 2.5 cm in diameter. This adequately covers an epithelioma 1 cm in diameter. It is not adequate for larger epitheliomas unless multiple exposures are given or the target-skin distance is increased. For this reason, the small size of the Philips tube is often inadequate and the size of the field covered by standard superficial therapy units is an advantage.

The rate of dosage is, of course, a little different with each technic. With my Philips apparatus it requires 3.5 seconds to deliver 1,000 r, whereas with the superficial therapy unit of 100 kilovolts it requires two and a half minutes to deliver 1,000 r.

As stated, the small dose less than 1 cm in depth of the radiation produced by the Philips tube makes it especially suitable for treatment of cancer of the eyelids. The ability to give large doses of this type of radiation within a few seconds is a great advantage in treating lesions on the lids because one cannot hold the lids still long. Also, the eyeball can be successfully shielded against contact roentgen therapy. These advantages give it great superiority over radium or roentgen rays produced by ordinary superficial therapy apparatus for the treatment of cancer of the eyelids.

TREATMENT OF HEMANGIOMA

By using the tables of Paterson and Parker,⁶ the output in gamma roentgens of small radium applicators, which I have used repeatedly for the treatment of hemangiomas, may be calculated. One of these applicators is rectangular and measures 1.5 by 3 cm and is composed of three silver tubes within a brass tray, which gives a total filtration equivalent to 2 mm of brass. This applicator contains 90 mg of radium and is used at a distance of 1 cm on a balsam wood block. The period for the erythema dose is three and a half hours and for the therapeutic dose for hemangiomas two and a half hours. The output of this applicator, as computed from the charts of Paterson and Parker, is 675 gamma roentgens in two and a half hours at a distance of 1 cm. Another radium applicator I use is 2 by 4 cm and contains 75 mg in silver tubes in a brass box. It is applied at a distance of 1 cm for three and a half hours for the treatment of angiomas. This dose is

⁶ Paterson, R., and Parker, H. M. Dosage System for Gamma Ray Therapy, *Brit J Radiol* 7 592-632, 1934.

computed to be 655 roentgens. Such a treatment is applied at intervals of three months three to five times on thick or deep hemangiomas, or fewer times on more superficial ones. When I refer to thick or deep angiomas, I mean those between 5 and 10 mm thick. For deeper ones I may use implants. For the more superficial, radium plaques properly screened and in contact with the skin are best.

In the treatment of hemangiomas one is interested especially in the cosmetic result. This is a completely different objective from that in the treatment of epithelioma, in which the cure rather than the appearance is paramount. To obtain a good cosmetic result the aim should be to avoid local cutaneous reactions. Hence the erythema dose which is obsolete in the treatment of cancer is important in the treatment of hemangiomas and some other cutaneous diseases. The aim is to cause the disappearance of the angioma while causing the least possible injury to the skin.

If the gamma rays of radium are used it takes about 1,000 r to produce a perceptible faint erythema, whereas with the relatively soft radiation produced by the Philips tube filtered through 2.5 mm of aluminum a perceptible erythema is probably produced by about 300 r. One is able with the radium applicator to give doses of 675 r without producing an erythema, whereas only about one-half this amount with the Philips apparatus causes erythema. In other words, one can apply roughly three times as many gamma roentgens as roentgens from the Philips apparatus, if the erythema reaction of the skin is accepted as the limit.

The technic advised by Pendergrass⁷ for the treatment of hemangiomas with the Philips apparatus has formed the basis of my work. Using radiation filtered through 2.5 mm of aluminum he gives 200 to 250 r at intervals of six weeks for a total of four to six doses. This Philips technic gives a total dose of 1,000 to 1,500 r, which compares with a total dose of 2,250 to 3,750 gamma roentgens from the radium applicator. Each dose of 250 r from the Philips apparatus is equivalent to about three fourths of an erythema dose, whereas with the radium each dose of 675 r is roughly equivalent to two thirds of an erythema dose.

It appears from these figures that the quality of radiation from the Philips apparatus is not as suitable as that from radium applicators for the treatment of hemangiomas. Likewise it seems that the harder radiation from the Chaoul tube would be superior to the radiation from the Philips tube for this purpose. I believe that Dr. Pendergrass prefers and generally uses the Chaoul tube.

7 Pendergrass, E. P., and Hodes, P. J. Further Experiences with Chaoul Therapy, *Radiology* **37** 550-559, 1941.

These conclusions are in line with my clinical experience⁸ and with that of many other radiologists and dermatologists Pfahler⁹ stressed the importance of the hard quality of radiation in the gamma rays of radium for the treatment of hemangiomas. As he stated, "Some good results have been obtained and reported by various authors with each kind of radiation—high voltage and high filtration, low voltage and moderate filtration and contact therapy with very low voltage and little filtration." Pfahler stated that it was his impression that for the treatment of hemangioma the highly filtered radium rays (gamma rays) give the most uniformly good cosmetic results. MacKee¹⁰ also favored radium for the treatment of hemangiomas, but preferred less filtration.

TREATMENT OF WARTS

The Philips tube is specially useful in the treatment of warts, because of the large output. The average dose unfiltered for small warts is 2,500 to 3,500 r. This is delivered in a few seconds. Fortunately, the soft quality of the radiation and the short distance eliminate worries about deep injuries which may follow the use of higher voltages and longer target-skin distances. For plantar warts a dose of 3,500 r is often used advantageously.

TREATMENT OF KERATOSES

For the treatment of senile and seborrheic keratoses, the average dose is 1,200 r unfiltered. The skin about the keratosis is closely shielded. The cosmetic results from this treatment are good.

MECHANICAL CONSIDERATIONS

The chief advantage of the Philips tube, like the Chaoul tube, lies in the tremendous output made possible by the short target-skin distance. It saves a great deal of time. Also, the absorption of the major portion of the output within the upper centimeter of tissue gives relative protection to deeper structures.

Both Braestrup and Quimby have warned that considerable amounts of stray radiation develop around the Philips tube. The operator, to be safely protected, must wear a lead-rubber fluoroscopic apron and lead rubber gloves whenever near the tube during treatments if more than two or three are given daily.¹¹

8 Andrews, G. C. *Diseases of the Skin*, ed 3, Philadelphia, W. B. Saunders Company, 1946, *Treatment of Angioma Based on Ten Years' Experience at the Vanderbilt Clinic*, *Arch Dermat & Syph* **37** 573-582 (April) 1938.

9 Pfahler, G. E. *The Treatment of Hemangioma*, *Radiology* **46** 159-170, 1946.

10 MacKee, G. M. *X-Rays and Radium in the Treatment of Diseases of the Skin*, ed 3, Philadelphia, Lea & Febiger, 1938.

11 Stenstrom, W., Quimby, E. H., and Pendergrass, E. P. *Report of Research and Standardization Committee*, *Am J Roentgenol* **43** 118-125, 1940.

The Philips apparatus is portable. This feature is of little practical value. If the portable feature were done away with and safety and stability were substituted for it by the use of a protective screen and a different tube stand, wider use of the apparatus would be encouraged.

The dental type of extension of the tube stand is cumbersome and unreliable, because it is so weak that the weight of the cable continually pulls the tube out of position. A good counterbalanced tube stand, such as the Chaoul or Solus machines have, would improve the Philips apparatus.

The smaller cones with the Philips machines are of little value. I have observed that accurate treatments can be made only if the patient lies down on a table and if the lesion is exposed through a hole cut in a piece of sheet lead, using a cone far larger than the size of the lesion. Then if the patient or the tube moves a fraction of an inch, the lesion remains in focus.

Aside from these shortcomings, the Philips tube and apparatus possess exceptional merits for the treatment of small superficial epitheliomas and hemangiomas and for the treatment of keratoses and warts. It has special advantages for the treatment of epitheliomas on the eyelids.

DISCUSSION

DR. ANTHONY C. CIPOLLARO, New York. We have been fortunate in hearing Dr. Andrews, who simplified a complicated subject. I would like to discuss contact therapy for a few minutes. What will it do for dermatology? Dr. Andrews has already pointed out its limitations. It has some uses, but the uses are limited to a few localized diseases like the epitheliomas and the hemangiomas.

We have here essentially an x-ray machine which delivers radiation of approximately 50 kilovolts. In that respect it is just like any ordinary x-ray machine if it is throttled down to 50 kilovolts, and so the effects to be expected from its use in contact therapy should be the same as those to be expected from an ordinary x-ray machine.

When Chaoul first advocated this method of therapy, he had three things in mind. First, he wanted to save time. He wanted to deliver a great many roentgens in a short period of time. Who wants to give 8,000 roentgens in one minute for a cutaneous disease, even a basal cell epithelioma? Certainly, one would not think of treating an epithelioma in the office with 8,000 roentgens all at one time. Second, it is difficult to measure time with exposures of such great intensity unless one has a special clock or automatic timer which measures in one twentieth of a second. The second reason that Dr. Chaoul advocated the use of this type of therapy is that he desired to limit the radiations to a well circumscribed volume of tissue. By so doing, destructive caustic doses of roentgen rays are applied to the diseased parts and the surrounding normal tissues escape damage. Third, Chaoul thought that the results with contact therapy were similar to those obtained with radium and superior to those obtained with conventional roentgen ray therapy. He ascribed this superiority to the fact that radium and

contact therapy were applied close to the skin. Most radiologists and dermatologists agree that a lesion responds equally well to either form of radiation provided that it is properly administered.

DR. GEORGE CLINTON ANDREWS, New York. One purpose I had in presenting this paper was the hope that the manufacturers of the Philips apparatus might improve this machine.

The principle of using a short target-skin distance, and thereby protecting the deeper structures, is an excellent one.

There is a great deal of stray radiation, which necessitates wearing a lead-rubber apron and lead-rubber gloves. Also, the tube holder is a flexible extension of the type used in dental apparatus, which leads to inaccuracy because the heavy weight of the cables pulls the tube out of position.

LUPUS ERYTHEMATOSUS TELANGIECTODES

PAUL E BECHET, MD

ELIZABETH, N J

IN 1888 Radcliffe Crocker¹ first described a telangiectatic form of lupus erythematosus characterized by symmetric persistent circumscribed patches on both cheeks, which on palpation were decidedly thickened and shot through with dilated blood vessels. The extensor surface of the hands was the seat of patchy persistent erythema, resembling chilblain, which after involution showed atrophic scarring. According to Crocker the patches on the cheek simulated the red paint on a clown's face. Under the term "erysipelas perstans faciei," Kaposi,² in 1872, also called attention to the deep red patches on the face with purpura preceding the onset of lupus erythematosus acutus disseminatus.

For the past thirty-five years, with one exception no articles on the subject have appeared in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, and there are not more than seven unchallenged case reports in that journal. It is not described in the textbooks with the exception of Ormsby's book,³ in which it has been given a paragraph. There is a report of a fatal case of lupus erythematosus acutus disseminatus with disseminated telangiectasis by Robertson and Klauder,⁴ who stated, "The association of disseminated telangiectasis with lupus erythematosus has not, to our knowledge, been reported in the literature." The patient had a patch of lupus erythematosus discoides on her scalp for three years before the appearance of purplish telangiectatic patches on her breasts, which gradually spread to the abdomen and legs. Shortly thereafter the face became the site of irregular ovoid scaly lesions of a rosy pink color and somewhat infiltrated. They were of the discoid type but later spread over the entire face and neck, becoming erythematous and of such a deep red color as to resemble the eruption in erysipelas. Death

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 13, 1946

1 Crocker, H. R. Diseases of the Skin. Their Description, Pathology, Diagnosis and Treatment, Philadelphia, P. Blakiston Son & Co., 1888

2 Kaposi, M. Neue Beiträge zur Kenntniss des Lupus erythematosus, Arch. f. Dermat. u. Syph. 4: 36-78, 1872

3 Ormsby, O. S. A Practical Treatise on Diseases of the Skin, Ed. 5, Philadelphia, Lea & Febiger, 1937

4 Robertson, W. E., and Klauder, J. V. Lupus Erythematosus Acutus Disseminatus. Report of Fatal Case Associated with Disseminated Telangiectasis, Arch. Dermat. & Syph. 8: 487-497 (Oct.) 1923

occurred three and one-half years after the appearance of the disease on the scalp, five months after the incidence of the discoid lesions on the face and six weeks after the appearance of constitutional symptoms

At a meeting of the Chicago Dermatological Society, Harry R Foerster⁵ presented a case for diagnosis. The patient had had advanced pulmonary tuberculosis which was apparently quiescent. The cutaneous lesions first appeared on the feet and later on the hands and face. Their appearance varied in intensity, becoming worse in hot weather, and consisted of cyanotic streaks and blotches. Small horny plugs formed on the lateral and the plantar surfaces of the feet. The lesions were painful. The facial lesions consisted of pigmented inflammatory telangiectatic and scaly macules. The ears, face, trunk, palms and soles showed more or less pronounced telangiectasia. In the discussion Ormsby stated that the clinical picture was one of vascular disturbance of the skin due to tuberculosis, and whether it was called lupus erythematosus, lupus pernio or sarcoidosis did not matter. Finnerud also stated the belief that the condition was due to tuberculosis but considered the clinical picture as atypical lupus erythematosus. Foerster, in closing, stated that the condition was considered a telangiectatic form of lupus erythematosus with a toxemia of underlying tuberculosis as the causative factor. Ormsby⁶ presented a case for diagnosis at the clinical session of the Dermatological Conference of the Mississippi Valley Dermatological Society in Chicago. The patient, a woman, was first seen nine years previously. At that time there was moderate erythema with scaling and telangiectasia on both cheeks and on the forehead. Subsequently, punctate atrophic lesions developed. For a year prior to presentation the patient had been given gold sodium thiosulfate with good results, the active process had disappeared, and only the atrophy and the telangiectasia were present. In the discussion Pusey and Michelson suggested the diagnosis of telangiectatic lupus erythematosus, which was accepted by Ormsby. Ormsby⁷ later presented another case in a man aged 53. His cheeks were covered by a symmetric eruption consisting of pale red elevated plaques, at the margins of which were innumerable dilated blood vessels. The nose, chin and neck were also the site of similar lesions but much smaller in size. In closing the discussion Ormsby stated, "The striking characteristic in this case was the enormous number of dilated blood vessels. Telangiectatic lupus erythematosus is comparatively rare. It is somewhat difficult

⁵ Foerster, H R. A Case for Diagnosis (Lupus Erythematosus, Telangiectasia), *Arch Dermat & Syph* **15** 72 (Jan) 1927

⁶ Ormsby, O S. A Case for Diagnosis, *Arch Dermat & Syph* **20** 388 (Sept) 1929

⁷ Ormsby, O S. Lupus Erythematosus Telangiectodes, *Arch Dermat & Syph* **22** 189 (July) 1930

to place the present case exactly, that is, to say whether it is the telangiectatic type of the disorder or whether the telangiectasia is a complication in an ordinary case. As the symptoms of the disease cleared under treatment with a gold compound the blood vessels also disappeared. This seems to show that they were involved by a common process."

Michelson's⁸ case of lupus erythematosus of the telangiectatic type presented before the Minnesota Dermatologic Society occurred in a farmer aged 21, who presented a diffuse telangiectasis of the face and neck and to a lesser extent of the hands. Erythema and atrophy were also present. The biopsy showed an atrophic epidermis, dilated superficial vessels and a slight amount of infiltration in the papillary portion of the corium. In the discussion Montgomery stated that the histologic picture supported the diagnosis. Combes'⁹ case was presented before the New York Dermatologic Society. The patient, a boy aged 17, had well defined erythematous patches scattered over the face and the ears. They consisted almost entirely of fine telangiectases with central atrophy. "There was no scaling and only on the nose was there follicular patulance." Both ears were covered with telangiectases interspersed with atrophy. An interesting case was exhibited at the Chicago Dermatological Society by Brunsting and Nomland¹⁰. The patient was a girl aged 15 with the diagnosis of lupus erythematosus (telangiectatic type), epithelioma (basal cell) and hematoporphyrinuria. There was a history of sensitivity to light and an epithelioma about 5 mm in diameter on the left side of the nose. The eruption had begun at the age of 1 year. At the time of presentation there were sharply defined red patches on the cheeks, forehead, nose and chin with no scaling, but telangiectasia could be discerned in many places. In the discussion Ormsby stated that he had observed the patient when she was 18 months old and that time had demonstrated the correctness of the diagnosis of lupus erythematosus. Montgomery said that when the patient was at the Mayo Clinic a biopsy revealed the histologic picture of subacute disseminated lupus erythematosus. Gilman's¹¹ case of telangiectatic lupus erythematosus was presented before the Philadelphia Dermatological Society. The patient, a man aged 27, presented on both sides of the face a blotchy reticulated telangiectasia. Atrophy, scaling and pustulous follicular plugs were absent. The diagnosis was not questioned in the discussion.

8 Michelson, H. E. Lupus Erythematosus Telangiectatic Type, *Arch Dermat & Syph* **22** 530-531 (Sept) 1930

9 Combes, F. C. Lupus Erythematosus (Telangiectatic Type), *Arch Dermat. & Syph* **23** 572 (March) 1931

10 Brunsting, L. A., and Nomland, R. Lupus Erythematosus (Telangiectatic Type), Epithelioma (Basal Cell), Hematoporphyrinuria, *Arch Dermat & Syph* **27** 1035 (June) 1933

11 Gilman, R. L. Telangiectatic Lupus Erythematosus, *Arch Dermat & Syph* **38** 265 (Aug) 1938

An analysis of the 8 bona fide cases of lupus erythematosus telangiectodes appearing in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in over three decades is extremely interesting. It is significant that in the description of the first observation of this variant Crocker¹ mentioned the fact that besides the telangiectatic fiery red patches on the face there was present on the extensor surfaces of the hands a patchy persistent erythema, resembling chilblains, which after involution showed atrophic scarring. Kaposi,² also, called attention to the deep red patches on the face with telangiectasis preceding the onset of lupus erythematosus disseminatus in his first patients with this condition. Robertson and Klauder's⁴ fatal case of the disseminated type, which began as typical lupus erythematosus and later developed into widespread telangiectatic patches with the characteristic fiery red plaques on the face, first described as "erysipelas perstans faciei" by Kaposi, corroborates the observations in Kaposi's first report of cases of the disseminated type.

Among the cases previously described which can be placed in the category of the acute or subacute disseminate type are those of Foerster,⁵ Robertson and Klauder⁴ and Michelson.⁸ The 2 cases presented by Ormsby and those shown by Combes, Gilman and Brunsting and Nomland were of the discoid variety of telangiectatic lupus erythematosus.

Ormsby's definition of the telangiectatic discoid type of lupus erythematosus clearly and accurately describes its symptoms, yet it was my privilege to observe a patient some time ago who presented a clinical picture of undoubted lupus erythematosus telangiectodes of the discoid type which differed entirely from cases previously reported.

REPORT OF A CASE

The patient, a white woman aged 42, stated that the oldest spot appeared on her nose about a year previous to her first visit. Shortly thereafter she noted an extension of the disease on her forehead and cheeks. The lesions consisted of sharply defined patches of a light to yellowish pink color, measuring 6 to 12 mm in diameter and numbering about a dozen. They were discrete and not confluent. A furfuraceous scaling occurred on some. Each one showed small telangiectases radiating to the periphery of each patch, where they ended abruptly. The normal skin did not present any dilated blood vessels. A thin atrophy was observed in a few of the lesions. All the patches presented the same clinical picture with only slight variations in scaling and in atrophy. Patulous follicular openings, keratotic plugs, infiltration, scarring and adherent scales were absent. The scalp was entirely free of seborrhea and presented a normal appearance. There were no lesions elsewhere than on the forehead, nose and cheeks.

The clinical picture differed so much from guttate morphea that that diagnosis was untenable. The diagnosis of lupus erythematosus telangiectodes was based on the atrophy, slight scaling, distribution, color and the presence of telangiectases, limited entirely to the lesion itself. Because of extremely small veins, intravenous aurotherapy, unfortunately, could not be used, but the patient was given weekly intramuscular injections of bismuth subsalicylate in doses of 2 grains.

(0.12 Gm) each. After a total of nineteen doses had been given there was a decided improvement of both the telangiectasis and the lesions. The patient disappeared from observation after the nineteenth injection. She consistently refused to be photographed, but she did permit a biopsy, and a histologic examination was made by Dr Wilbert Sachs, who reported that the microscopic diagnosis was lupus erythematosus. His description follows: "In the upper layer of the cutis and also about the adnexa was a moderate focal cellular infiltration. There was some interstitial edema and definite basophilic degeneration in the upper layer of the cutis. The overlying epidermis was irregularly acanthotic, the follicles were dilated. The granular and horny layers were retained except at the edge of the section, where there was some parakeratosis. The basal cell margin was intact and there was no edema. The cellular infiltration was composed of small, round and wandering connective tissue cells. There were no epithelioid, plasma or giant cells. The elastic tissue was clumped beneath the epidermis."

In a discussion of a paper by Goeckerman and Montgomery¹² entitled "Lupus Erythematosus. An Evaluation of Histopathologic Examinations," read before this association in June 1931, the late Dr David L. Satenstein stated, "My conception is that lupus erythematosus discoïdes is a chronic, for a variable time an acute, inflammatory process terminating in atrophy, that the atrophy is preceded by basophilic degeneration and disappearance of the elastic fibers, that without the degeneration a histologic diagnosis of lupus erythematosus discoïdes is not possible. Again, in those cases in which the epidermis is clinically not involved, and in which there is no scale or plug formation or hyperkeratosis, the basophilic degeneration is often the important factor in the diagnosis. I base my findings on a study of more than 100 cases of lupus erythematosus of the fixed type, without the basophilic degeneration, I do not make a diagnosis of lupus erythematosus discoïdes." I quote this statement of Satenstein's in full because his description of the characteristic microscopic picture in lupus erythematosus coincides with Sachs's observations in the case now under discussion. Dr Weidman kindly examined a section and wrote that the reaction in it was compatible with lupus erythematosus, but that he was not able to make that diagnosis from the section alone, but that this might be due to the fact that the section might not have included the typical and representative part of the lesion. I do not know whether or not the section sent Dr Weidman was the same one on which Dr Sachs's conclusions were based.

COMMENT

From the analysis and study of previous reports of cases, even though so few in number, one can arrive at certain conclusions based on the known facts of this variant of lupus erythematosus, namely, that the

12 Goeckerman, W. H., and Montgomery, H. *Lupus Erythematosus. An Evaluation of Histopathological Examinations*, Arch. Dermat. & Syph. **25** 304-314 (Feb.) 1932.

telangiectatic type of lupus erythematosus, though extremely rare, is a definite clinical variant and that it appears in the acute or subacute disseminate type as well as in the discoid type. That the telangiectasis is a part of the clinical picture is proved by its disappearance with the rest of the lesions after aurotherapy. Whether or not the variant now presented by me for the first time will find its place in the literature depends on future observers, because of the rarity of the condition it might take a long period of time.

1364 North Avenue

ABSTRACT OF DISCUSSION

DR. OLIVER S. ORMSBY, Chicago. I appreciate the paper of Dr. Bechet. It has called to attention a symptom complex which I believe is a variety of lupus erythematosus and is a distinct entity. In addition to the cases on record, I have seen a number of instances in private practice, and so I am sure that there is such an entity.

In the acute disseminated cases with telangiectasia, the telangiectasia appears to be more or less a secondary manifestation, and whether it should be called lupus erythematosus telangiectodes is a question. I have classed the telangiectatic variety with the discoid type, in which the face is largely the site of occurrence.

The case reported by Klauder (*ARCH. DERMAT. & SYPH.*, 8:487, 1923) in which telangiectasia later developed, illustrates the generalized form of the disease. Klauder believed this to be a representative telangiectatic form of disseminated lupus erythematosus.

The first case of lupus erythematosus which became disseminated was the case of Kaposi which has been cited. In a few of the cases of the disseminated type, telangiectasia has occurred as a complication, which shows that telangiectasia can be a part of the process. However, as I stated before, I believe that the term lupus erythematosus telangiectodes should be limited to the type that occurs on the face and on the neck and really belongs to the discoid group.

Dr. Bechet has made an admirable presentation of a rare form of lupus erythematosus, and I am sure that many more cases will be observed now that attention has been focused on this subject.

DR. FRED D. WEIDMAN, Philadelphia. Not that it means anything in the cure of the disease and probably not that it means much cosmetically in the case, but perhaps mainly for testing the value of the drug, I would like to mention rutin. It is employed in patients with high blood pressure. At a recent meeting of the Philadelphia Dermatological Society (to be reported in *ARCH. DERMAT. & SYPH.*) Dr. Klauder reported that the nosebleed in his patient had ceased after administration of rutin. It might be useful in dermatoses associated with telangiectasis and with purpuric hemorrhage.

DR. PAUL E. BECHET, Elizabeth, N. J. I have nothing to add, Mr. President, other than to thank you and Dr. Ormsby for the discussion.

HYPERSENSITIVITY TO SULFAPYRIDINE

Report of a Case

HARRY BELLACH, M D

NEW BRITAIN, CONN

THERE are few drugs to which some patient has not shown an idiosyncrasy or allergic hypersensitivity. The sulfonamide drugs have been notable as producers of hypersensitivity, and the literature contains numerous reports of such untoward reactions. It is well known that patients may manifest their hypersensitivity to these drugs by such reactions as various types of cutaneous eruptions, pruritus, angio-neurotic edema, depression of red and white blood cell counts and granulocytopenia with angina.

It has been reported that therapeutic or prophylactic desensitization, or more correctly hyposensitization, may at times be effected, but this cannot always be accomplished. The following case report represents an instance of a high degree of hypersensitivity to sulfapyridine and sulfathiazole.

REPORT OF A CASE

R D, a 28 year old white married woman, was admitted to the New York Skin and Cancer Unit of the New York Post-Graduate Medical School Hospital on Aug 16, 1946, for the diagnosis and treatment of a generalized pustular cutaneous eruption.

History—Three years before admission, in the third month of her first pregnancy, the patient had a few isolated pustules on the thoracic wall. There was rapid dissemination, so that in a few days the entire body, exclusive of the head and neck, was involved. The eruption persisted unchanged until three months postpartum, at which time it began to subside. Residual lesions remained on the lower aspects of the legs, soles, dorsa of both feet, and nail beds of the fingers and toes. The nails had been shed early in the course of the disease and never grew again.

In the first month of the second pregnancy, approximately one year later, there was an exacerbation of the eruption, but this was less extensive than the first attack. This continued at its height until two weeks before term, when the lesions cleared again, with the exception of those on the lower two thirds of the left leg and the nail beds of the fingers and toes. Four days postpartum the patient received penicillin to combat the residual lesions. Seven days after the start of penicillin therapy an acute and generalized exacerbation of the eruption occurred, accompanied with chills and fever. With the exception of the residual lesions previously mentioned, this subsided in six weeks with the local use of boric acid.

*From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology (Director, Dr Marion B Sulzberger), New York Post-Graduate Medical School and Hospital.

ointment The residual lesions remained unchanged and quiescent for approximately one year Two weeks before her admission 0.5 Gm of sulfapyridine four times daily, was administered On the seventh day following the institution of this medication, the patient's eruption became generalized and involved the entire skin exclusive of the scalp

Observations on Admission—Physical examination revealed a poorly nourished white woman, not appearing acutely ill Examination of the head and neck showed no abnormalities except for the presence of an upper artificial denture and several retained roots in the upper and lower jaws The scalp showed a mild seborrheic scaling The heart, lungs and abdominal viscera were normal The blood pressure was 114 systolic and 76 diastolic The extremities except for the lesions of the skin were normal

The urine was normal The blood cell count showed 4,130,000 erythrocytes, 12 Gm (72 per cent) hemoglobin and 13,250 leukocytes, with a differential count of 75 per cent polymorphonuclear cells, 20 per cent lymphocytes and 5 per cent monocytes The sedimentation rate (Westergren) was 74 mm in one hour Reactions to complement fixation and Kahn precipitation tests were negative

The skin of the entire body was involved in a polymorphous eruption The face was covered with a diffuse morbilliform erythema The neck, trunk and upper and lower extremities presented a great number of scaly crusted pustules on an erythematous base All finger and toe nails were absent, and the nail beds encrusted

Material obtained from the pustules was placed on different mediums and attempts made to culture micro-organisms aerobically, anaerobically and under reduced oxygen tension All cultures remained sterile No abnormalities were observed when the material was studied for the presence of fungi and viruses

Diagnosis, Course and Treatment—A definitive diagnosis was not made impetigo herpetiformis and acrodermatitis continua of Hallopeau were considered as the most likely diagnoses The treatment consisted of a wide variety of medications, systemic and topical, without notable improvement Streptomycin, given orally and parenterally, dihydrotachysterol ("hytakerol"), chorionic gonadotropin, estrogenic hormone, bismuth subsalicylate in oil, bismuth sodium triglycollamate ("bistrimate"), carbarsone, para-aminobenzoic acid, artificial fever therapy, vitamins and the extraction of retained dental roots were among the many therapeutic measures which failed to exert a favorable influence on the course of the disease

Reactions to Sulfonamide Drugs—On November 1, the patient received 10 Gm of sulfapyridine with equal amounts of sodium bicarbonate every four hours After three doses (30 Gm) it was necessary to discontinue the drug because of the severe reaction There was intense erythema of the face with edema of the upper lip, nose, eyelids and temples, and diffuse erythema of the rest of the body In addition to an increase in the number and size of the pustules in the sites formerly involved (legs and feet), there were numerous lakes of pus measuring 3 to 4 cm in diameter, scattered over the trunk The patient appeared acutely ill and remained so for three days, with a temperature elevation ranging between 100.2 and 104.4 F and a pulse rate of 110 to 160 On a regimen of diphenhydramine hydrochloride ("benadryl hydrochloride") 50 mg every four hours and topical applications of calamine emulsion and wet dressings, this acute episode subsided within six days of its onset

Since it was thought that this acute exacerbation was a manifestation of hypersensitivity to sulfapyridine, an attempt was then made to desensitize the patient On November 13, after the administration of 5 mg (0.005 Gm) of sulfapyridine, the patient complained of slight itching of the skin and erythema of the trunk

There was a mild exacerbation of the pustules on the legs and feet, but no febrile response. Repetition of the same dose the following day produced a similar reaction.

On November 20, 1 mg (0.001 Gm) of sulfapyridine was administered and the patient was observed closely for manifestations of hypersensitivity. Two and one-half hours after ingestion the patient experienced itching of the forearms, which was followed by erythema. One hour later (at three and one-half hours) erythema appeared on the neck and trunk, two and one-half hours later (six hours after ingestion of sulfapyridine) the posterior aspects of both thighs were similarly involved, with erythema of the face three hours later. Determinations of sulfapyridine levels in the blood were made on specimens drawn hourly for four successive hours after ingestion of the drug. Sulfapyridine was not detected in any of the specimens. On the following day (November 21) the erythema subsided somewhat, but new pustules appeared on the arms and trunk, while those on the left foot seemed to be undergoing involution. On November 22 (two days after the administration of the 1 mg test dose) there was complete disappearance of the erythema and drying of the pustules, indicating a remission of the reaction.

From the foregoing observations it was concluded that the patient had a great degree of hypersensitivity to sulfapyridine and that hyposensitization was not feasible. In the attempt to determine whether there was a similar hypersensitivity to other members of the sulfonamide drug group, the patient was given 15 mg (0.15 Gm) of sulfathiazole on November 29, at a time when the original eruption was in a quiescent state. Three hours later a pricking sensation of the back and arms was noted, which in the course of the next three hours was followed by erythema of the trunk and upper extremities. This was not accompanied with fever or new pustules. The blood cell count at this time showed no essential change from that found on admission. There were 4,050,000 erythrocytes, 11.8 Gm (71 per cent) of hemoglobin and 13,750 leukocytes, with a differential count of 80 per cent polymorphonuclear cells, 1 per cent eosinophils, 15 per cent lymphocytes and 4 per cent monocytes.

In view of this additional evidence of the patient's intolerance to the sulfonamide drugs, attempts at treatment with this group of drugs were abandoned.

COMMENT

According to the criteria set down by Sulzberger,¹ the condition in the case presented here falls into the class of an allergic eruption due to drugs, as a result of extreme hypersensitivity to sulfapyridine. In this connection it is particularly worthy of note that there was a seven day incubation period before the explosive outbreak following the first administration of a sulfonamide drug. After the sensitization had been established, the subsequent reactions occurred within a few hours after the administration of minute amounts of the drug. In contrast to these observations of chronologic intervals characteristic of allergic sensitizations, reactions were noted within twenty-four hours in patients

1 Sulzberger, M. B. *Dermatologic Allergy*, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 38.

receiving sulfonamide drugs for the first time in the 3 cases reported by Carpenter and Gorsuch² as bacterids which flared up after the administration of the drugs

It is conceivable that the present case is an instance of aggravation of a "bacterid" by sulfapyridine. However, it is unlikely that 1 mg of the drug, diluted and distributed throughout the body, could have sufficient bacteriostatic or bacteriocidal action to release sufficient bacterial substances to produce the severe generalized reactions. Herxheimer-like reactions may well occur in some cases, but in the case herein presented this could not be expected since the doses of the sulfonamide drugs were so far below the usual therapeutic levels

SUMMARY

A case of extreme hypersensitivity to sulfapyridine is presented. A similar intolerance to sulfathiazole in the same patient was demonstrated. Several possible mechanisms of the reactions noted are discussed, and the conclusion is reached that specific allergic sensitization is the most probable.

2 Carpenter, C. C., and Gorsuch, L. P. Bacterids Provoked by Internal Sulfonamide Administration, U. S. Nav. M. Bull. **44** 681, 1945

LICHEN PLANUS PEMPHIGOIDES

Report of a Case and Discussion of the Literature

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ERUPTIONS of lichen planus associated with vesicles, although not common, are not a great rarity. The vesicles may be few and scattered and of small size, or there may be multiple crops of vesicles and even large bullae. Reports of this form of eruption have appeared in the literature since 1881 when Baker (Crocker¹) was credited as having first described such a complication of lichen planus. Kaposi² has been generally credited with the origin of the term lichen ruber pemphigoides and with the first description of an extensive bullous eruption occurring in lichen planus. Kaposi stated that while he had seen lichen planus associated with pea-sized vesicles, he had never previously seen large bullae in lichen planus. He apparently coined the term lichen ruber pemphigoides to segregate this eruption of bullous lichen planus from the commoner vesicular lichen planus.

The term lichen ruber pemphigoides, or lichen planus pemphigoides, has been used somewhat loosely, in that some of the dermatoses described under this term showed little resemblance to pemphigus but were actually severer degrees of the vesicular manifestation. Other cases described under this title, in which there were multiple large bullae and mild to severe constitutional symptoms, were really pemphigus-like. In some cases the bullous eruption so dominated the clinical picture that the observers of such cases wondered whether they were not dealing with two disease entities, i e, pemphigus and lichen planus, occurring simultaneously. Kaposi² recorded this uncertainty, as did others³.

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1 Crocker, H. R. Lichen Planus. Its Variations, Relations and Imitations, *Brit J Dermat* **12** 428 (Dec) 1900.

2 Kaposi, M. Lichen ruber pemphigoides, *Arch f Dermat u Syph* **24** 344, 1892.

3 (a) Pautrier, L. M. Lichen plan complique d'eruption bulleuse (association de lichen plan et de dermatite polymorphe de Duhring-Brocq? ou lichen ruber pemphigoides?), *Bull Soc franç de dermat et syph (Reunion dermat)* **40** 1137, 1933. (b) Senear, F. E., in discussion on Stillians, A. W. Lichen Planus, *Arch Dermat & Syph* **22** 345 (Aug) 1930. (c) Zuger, I., and Gross, P. P. Bullous Lichen Planus with Recovery Following Use of Estrogenic Hormone, *Pennsylvania M J* **47** 571 (March) 1944.

Finger⁴ and Schriener⁵ suggested that bullous and vesicular lichen planus be divided into two groups. The first should include lichen planus in which vesicle formation was not extensive, of short duration and thus of little moment. The other group should consist of cases in which formation of bullae was extensive and the dominant feature. Schriener also specified that in order to be included in the latter group, vesicles and bullae should be present on skin uninvolved with lichen planus papules as well as on the papules. Pautrier,⁶ in discussing the subject of bullous lichen planus in "Nouvelle Pratique Dermatologique," distinguished between the two types. From a review of the cases of bullous lichen planus described in the literature, it appears that vesicle and bulla formation may vary considerably in degree and that cases have been recorded which represent transitions between the two suggested groups. In a complete review of the subject Straus⁷ avoided this division and discussed the whole subject under the title "Vesicular and Bullous Lichen Planus." However, the severer types of bullous lichen planus have a fairly definite course and usually present unique features and therefore seem worthy of some segregation as suggested by the older authors.

REPORT OF A CASE

J S, a 49 year old white man, whose occupation was that of a business executive, was a private patient of Dr Marion B Sulzberger, who has authorized me to publish this report. Fifteen years prior to hospital admission the patient had noticed a single lesion on the dorsum of his hand. After a clinical diagnosis of lichen planus had been made, low voltage roentgen therapy produced rapid involution of this early lesion. The same sort of eruption appeared five years later and disappeared spontaneously shortly thereafter. In January 1947 a second recurrence was manifested by lesions on the dorsa of the hands and on the forearms and legs. Examination at this time showed typical lichen planus papules on the areas mentioned. Administration of "bistriurate" (sodium bismuth triglycollamate) (Carroll Dunham Smith Pharmacal Co) 6 tablets daily (450 mg of elemental bismuth daily) was begun on January 27 and was continued somewhat irregularly over a period of seven weeks. The eruption spread to the thighs and upper portions of the arms during the treatment. Therefore, on March 13 the bistriurate was discontinued and arsenical therapy was started. A solution containing 2 per cent of arsenic trioxide and 1 per cent phenol in distilled water was given subcutaneously in graduated daily doses, beginning with 0.1 cc and increasing 0.1 cc daily. After the eighth injection, when a total of 0.036 Gm of arsenic trioxide, or 0.0273 Gm of metallic arsenic, had been given, the arsenic solution was discontinued because a low grade

⁴ Finger, E. Ueber Lichen ruber pemphigoides, Wien med Wchnschr **54** 157 (March) 1904.

⁵ Schriener, K. Lichen ruber pemphigoides, Arch f Dermat u Syph **161** 647 (Aug) 1930.

⁶ Pautrier, L. M. Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol 8, p 458.

⁷ Straus, M. J. Vesicular and Bullous Lichen Planus, Acta dermat venereol **14** 447 (Dec) 1933.

fever and edema of the lower legs suddenly developed. The lichen planus eruption continued to advance rapidly, and scattered papules and erythematous areas soon involved all parts of the body surface except the face. The lesions itched severely. 2, 3 dimercaptopropanol (BAL) therapy was initiated on March 29, and the patient received a total of 30 Gm in seven days. On April 2 a few scattered vesicles appeared on the legs. The eruption continued to become worse, and on April 7 the patient was admitted to the hospital. The legs, feet and ankles were moderately edematous, and there was mild edema of the eyelids. The entire integument was erythematous, and there was a morbilliform papular eruption of deeper hue on the anterior and posterior aspects of the trunk. Typical lichen planus papules were present on the shoulders, ankles, anterior aspect of the chest and dorsa of the hands. The skin of the extremities was scaling mildly. On the legs there were a few scattered bullae up to 2 cm in diameter, which were tense with clear fluid. A fine grayish reticulation typical of lichen planus was seen on the buccal mucosa. On admission the temperature was 101 F. The febrile course was remittent and gradually abated to normal in about a week. The maximum temperature was 103.4 F.

Laboratory Data—The sedimentation rate of erythrocytes was 16 mm per hour (Wintrobe method). The blood nonprotein nitrogen was 280 mg, total serum cholesterol 1100 mg, icterus index 50, total serum protein 63 mg, serum albumin 44 mg, serum globulin 19 mg, cephalin-cholesterol flocculation plus-minus and urine urobilinogen 100 mg, and several urinalyses showed no deviation from normal except an occasional faint trace of albumin. The urinary excretion of arsenic was 0.08 mg of arsenic trioxide in twenty-four hours (total quantity of urine 8400 cc). On April 8 the red blood cell count was 4,630,000 and the white blood cell count was 7,000, with 62 per cent polymorphonuclear leukocytes, 3 per cent eosinophils, 29 per cent lymphocytes and 6 per cent monocytes. The following day the total white blood cell count was 10,200, with 79 per cent polymorphonuclear leukocytes, 9 per cent eosinophils, 8 per cent lymphocytes and 4 per cent monocytes. A roentgenogram of the chest showed no abnormalities.

From April 10 through April 15 the patient received daily plasma transfusions of 250 cc each. General supportive therapy was given, with mild local applications.

The erythema and morbilliform eruption gradually faded, and the edema slowly receded. The eruption of lichen planus papules became more or less generalized during the hospital stay. No new vesicles or bullae appeared, and the old ones healed. On April 21 the patient was discharged from the hospital.

The patient's general sense of well-being and energy gradually improved during his convalescence. He partly resumed his daily routine, but never returned to his normal activity. On about May 12 the patient observed a few bullae on the lower portions of the legs, which he described as ranging in size from that of a silver quarter to a half-dollar. During the next few days split-pea-sized vesicles appeared on the thighs, penis, forearms and face and in the mouth. After discharge from the hospital until the appearance of the new outbreak of vesicles and bullae, the patient had received no internal medication other than vitamin concentrates, yeast tablets and diphenhydramine hydrochloride ("benadryl hydrochloride").

The patient was readmitted to the hospital on May 28. At that time there were typical papules of lichen planus thickly distributed in plaques and scattered single lesions over the trunk, extremities and neck. The buccal mucosa displayed typical reticulated lesions of lichen planus. On the nose, chin, right elbow, umbilicus and fingers were fairly tense split-pea-sized vesicles with moderately thick walls. On the legs and feet were great bullae, ranging up to 5 cm in diameter. Most of the bullae contained clear fluid, but in some the contents were cloudy yellow. The

temperature was normal on admission, but an intermittent low grade fever began June 10 and continued throughout the remainder of his hospital stay. Daily peaks averaged 101.2 F.

Laboratory Data—The erythrocyte count ranged from 3,900,000 to 4,900,000, and the total leukocyte count varied from 8,650 to 13,550. The first differential count revealed 7 per cent eosinophils. This rose to a maximum of 31 per cent on June 24 and then receded to 15 per cent on the last differential count made. The

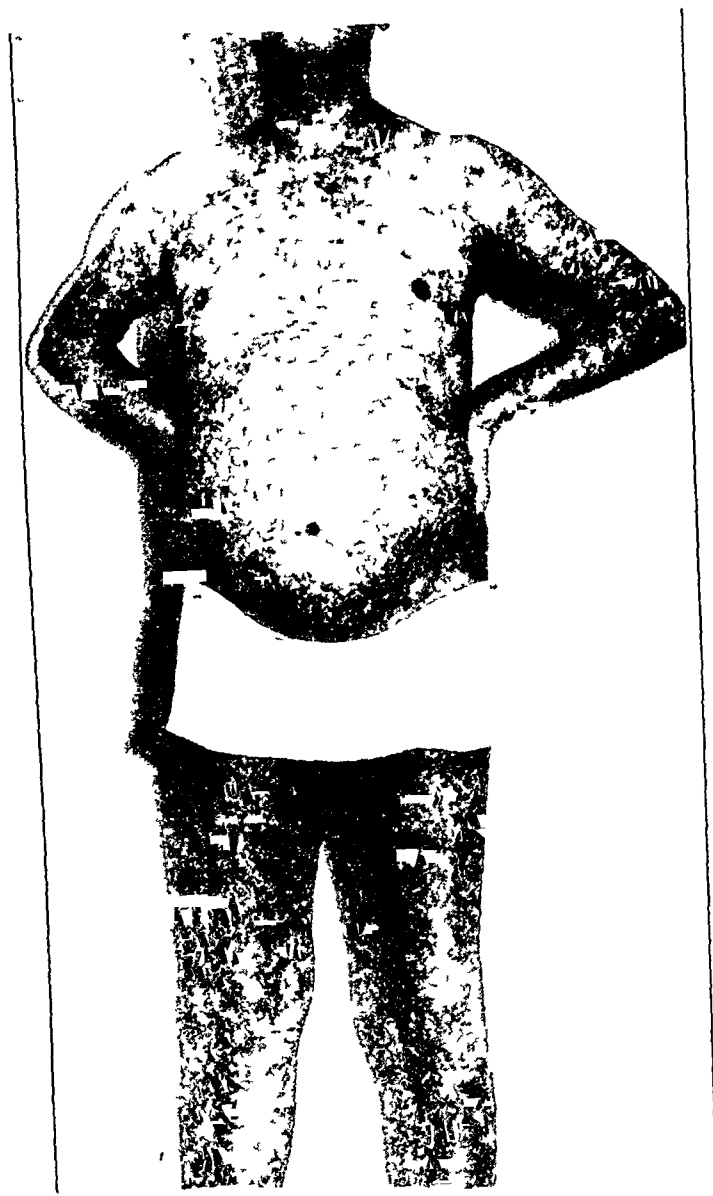


Fig 1—Photograph of the patient, J. S., showing extensive eruption with many ruptured bullae, pronounced hyperpigmentation and circumscribed depigmentations.

various differential counts were not remarkable otherwise. On June 4 the sedimentation rate of erythrocytes was 25 mm per hour (Wintrobe method). Eight urinalyses revealed nothing unusual. Aerobic and anaerobic cultures from the bullae remained sterile. On June 5 the total serum protein was 8.4 mg, with the serum albumin 5.0 and serum globulin 3.4 mg. The results of other laboratory tests made on the blood serum were as follows: cholesterol, 175 mg; calcium,

113 mg , inorganic phosphates, 37 mg , and alkaline phosphatase, 20 Bodansky units per hundred cubic centimeters Plasma carbon dioxide-combining power was 52.2 volumes per cent and the plasma chlorides were 620 mg per hundred cubic centimeters Smear of blister fluid displayed 4 per cent eosinophilic cells

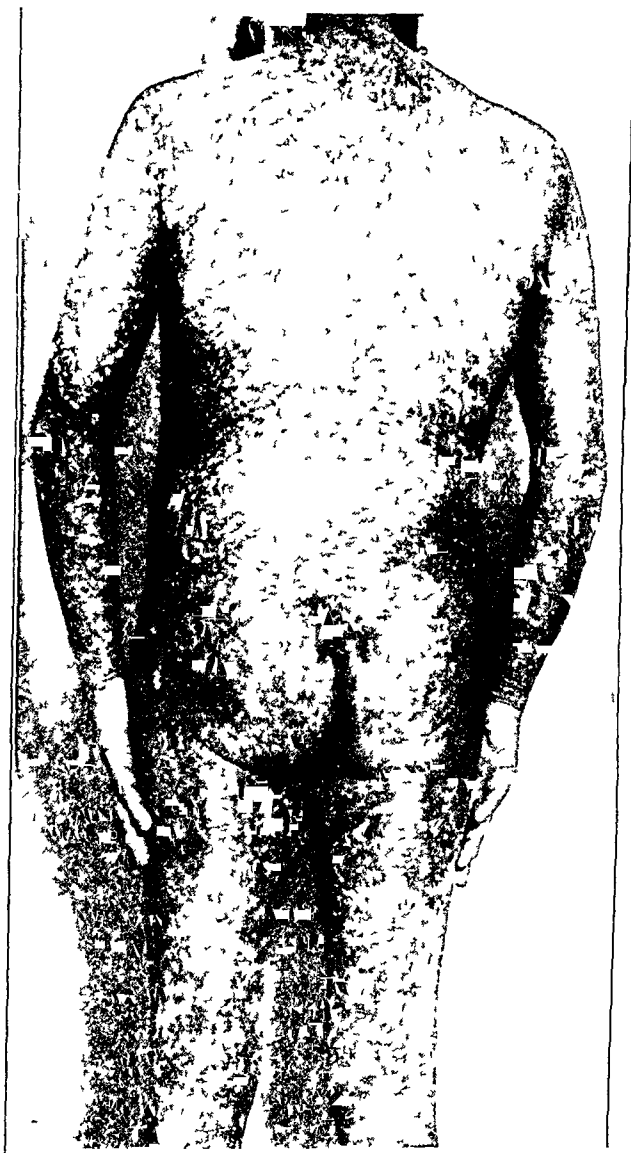


Fig 2—Photograph showing very extensive and characteristic eruption on back, buttocks and extremities

New crops of vesicles appeared almost daily They were usually preceded by attacks of severe itching, and there was a distinct tendency for the bullae to erupt in large groups They appeared on plaques of lichen planus, on individual papular lesions and also on apparently normal skin All parts of the body surface were involved intermittently except the back Vesicles frequently appeared on the eyelids

and about the alae nasi. Vesicles formed on the mucous membranes of the nose, mouth and pharynx. From time to time the patient coughed up blood-tinged sputum and shreds of tissue. He had intermittent hoarseness of varying degrees. No blood was ever observed in the urine or stools. The conjunctivas were never involved. Bullae were especially large on the thighs, the lower aspect of the legs and on the feet. In these locations they were frequently 3 or 4 cm in diameter. These blisters were not easily ruptured. After rupture an oozing erythematous base appeared which healed with less pigmentation than the surrounding skin and with a tendency to slight fungation and definite elevation above the adjacent skin.

Nikolsky's sign was positive on all areas of skin tested and throughout the entire period of the severe eruption.

At this time Dr. Warfield T. Longcope of Johns Hopkins Medical School saw the patient in consultation with Dr. Sulzberger. Because of the possibility that a

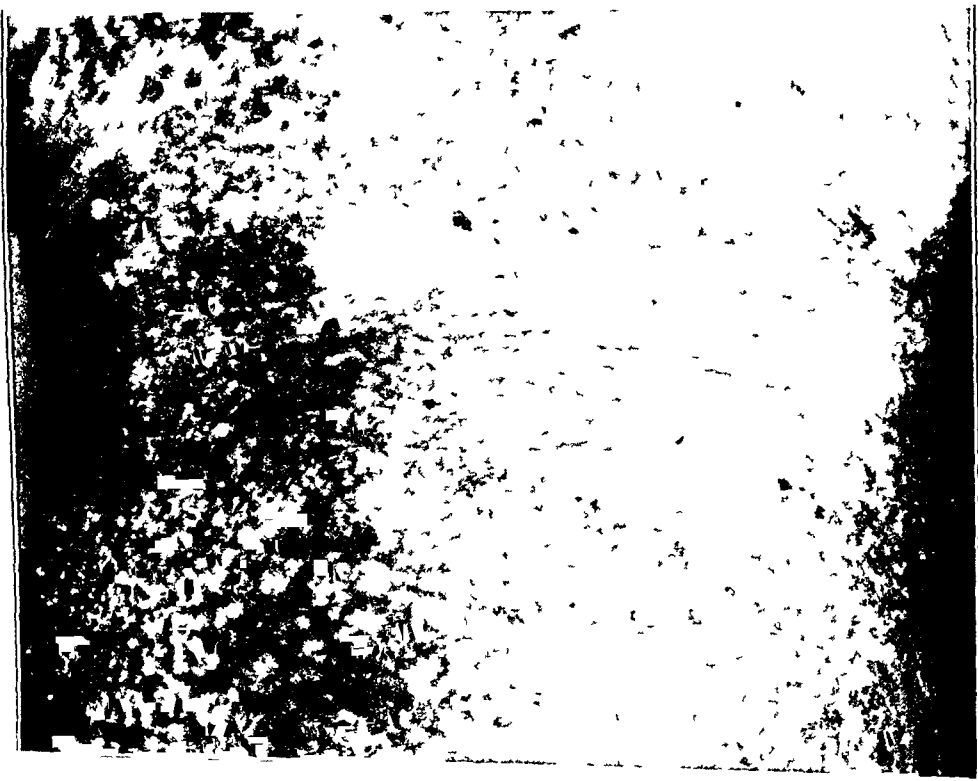


Fig 3—Close-up of abdomen and chest of the patient, J. S., showing vesicles, bullae, crusts and hyperpigmentation together with scattered depigmented and slightly elevated lesions at sites of old bullae.

remaining reservoir of arsenic might conceivably be responsible for the continuing bullous eruption, Dr. Sulzberger and Dr. Longcope agreed to administer BAL in oil once again. Two doses of BAL of 2 mg per kilogram of body weight were given four hours apart. After the second dose the patient had an attack of severe itching. Eight hours after the second dose, a third dose was given, and two hours later another episode of severe itching occurred. BAL therapy was then discontinued. Before BAL therapy the quantities of arsenic in twenty-four hour urine specimens were as follows: 0.02 mg as arsenic trioxide on May 31 and none on June 2 and June 6. (Normal excretion is less than 10 mg of arsenic as arsenic trioxide in twenty-four hours on an unrestricted diet.) The three doses of BAL were given on June 7. The twenty-four hour urine specimen on that day analyzed for arsenic revealed 0.07 mg of arsenic trioxide. The following results were

obtained on twenty-four hour specimens analyzed for arsenic on subsequent days June 8, 0.03 mg, June 9, none, June 10, none, June 11, 0.06 mg, June 13, none, June 16, none, June 18, 0.2 mg, and June 20 and 23, none. Estimations of blood arsenic levels were made by Dr. Alexander O. Gettler, professor of toxicology at the Medical College of New York University, with the following observations: 50 micrograms of arsenic (element) in 100 cc of blood on a specimen collected on June 19. (Normal range is 20.0 micrograms [0.020 mg] or less in 100 cc of blood.)

The reactions to the Pels-Macht test and the Macht-Astro test (phytopharmacologic tests) were negative for pemphigus on July 1.

A biopsy specimen was taken from the anterior aspect of the chest on June 2. The tissue included a vesicle which had arisen on apparently normal skin and an

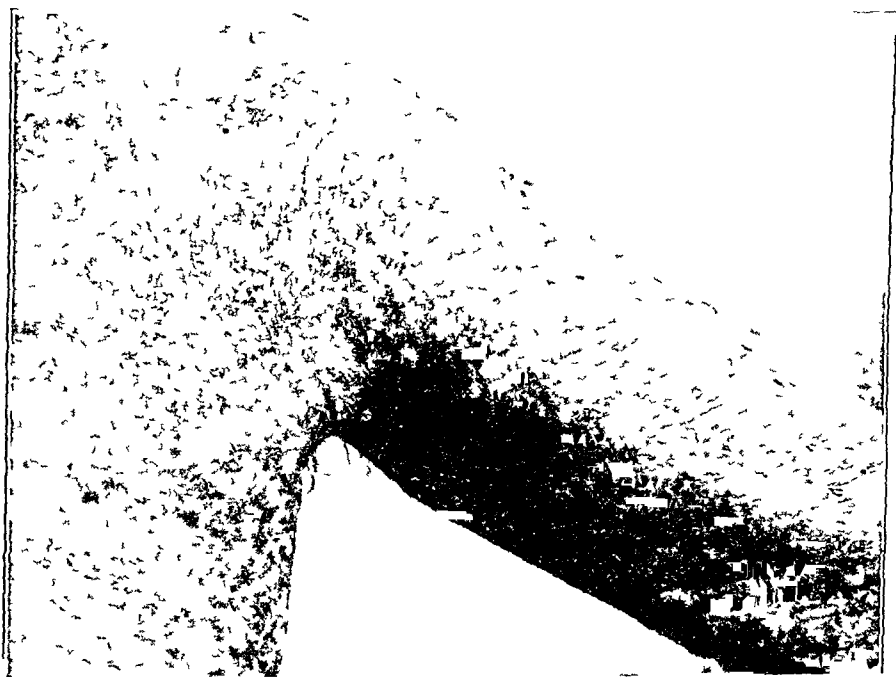


Fig. 4—Photograph showing detail of depigmented and slightly elevated sites of old ruptured bullae, with surrounding lichenification and hyperpigmentation

adjacent lichen planus papule. The histologic studies were made by Dr. Charles F. Sims, and his report was as follows:

The epidermis was flattened throughout a good part of the section and appeared to be separated from the underlying corium in the affected zone. There was a subepidermic bulla filled for the most part with fibrin and red blood cells, a few polymorphonuclear and small round cells and occasional eosinophils. The papillary bodies appeared fairly intact, and there was a diffuse cellular reaction in the papillary and subpapillary zones, composed of small round wandering connective tissue and occasional polymorphonuclear cells. Some scattered chromatophores were visible. The infiltration formed a more or less bandlike arrangement. The vessels of the upper part of the corium were dilated and surrounded by sparse cellular infiltration similar to that previously described. The microscopic diagnosis was lichen planus bullosus.

Although extremely itchy, in great suffering and very depressed, the patient at no time appeared to be dangerously ill. Except for the skin and mucous membranes, his general condition seemed good during his entire hospital stay. His appetite was fair, and during his sixty-five days in the hospital he lost only 8 pounds (3.6 Kg). He was allowed bathroom privileges at all times.

The following medications seemed to have no effect on the course of the disease: penicillin, 100,000 units by mouth every three hours for eleven days, sulfapyridine, 6 Gm daily for two days, streptomycin, 0.5 Gm every six hours for eight days, desoxycorticosterone in oil, 5 mg daily for forty-one days, mixed tocopherol, 300 mg daily for forty-three days, and sodium paraminobenzoate, 16 Gm daily for eight days.

On July 24, therapy with suramin sodium ("naphuride sodium," Winthrop-Stearns, Inc.), was initiated. The first day he received 0.1 Gm, the second day 0.2 Gm and 0.3 Gm was given on the third day. A dose of 0.3 Gm of suramin sodium was given three times weekly thereafter. After the third dose the crops of bullae were less extensive, and the individual bullae were smaller. The lichen planus papules also faded considerably, leaving brownish pigmented areas at their sites. Where bullae had healed recently, there were slightly elevated areas with less pigment than the surrounding skin. The patient improved generally and was discharged from the hospital on July 31.

Following discharge from the hospital the patient continued to show slow improvement. The vesicles and bullae continued to decrease in number and size. In the middle of August 1947 the patient had several large bullae on the legs, these lesions made their appearance over a period of two weeks and then healed. Small crops of vesicles appeared at infrequent intervals. By the middle of October 1947 all vesicles had disappeared, and afterward no new ones formed. Typical lichen planus lesions were widespread at the end of 1947, however, these too disappeared gradually. The hyperpigmentations slowly faded and the pruritus diminished. At the present writing (February 1948) the skin is essentially normal except for a very slight residual mottled hyperpigmentation on the thighs, arms and trunk. The patient is apparently entirely well and following his normal business, social and family activities.

COMMENT

In cases of vesicular and bullous lichen planus which have had previous arsenical therapy, the question always arises as to whether or not the bullae or vesicles are evidence of a reaction to arsenic. In 1902 Whitfield⁸ reviewed this aspect of the problem and listed several reports of bullous or vesicular lichen planus which had no arsenical therapy prior to the appearance of vesicles or bullae. There are other reports in the literature of this dermatosis in patients who had received no preceding arsenical medication.⁹ In some cases arsenic had been given while

8 Whitfield, A. A Note on the Occurrence of Bullae in Lichen Planus, *Brit J Dermat* **14** 161 (May) 1902.

9 (a) Crocker¹ (b) Schriener⁵ (c) Golay, J. La lichen plan bulleux, *Ann de dermat et syph* **8** 543 (Oct) 1927. (d) Wise, F., and Eller, J. J. Bullous Eruptions in Hemorrhagic Sarcoma of Kaposi and in Lichen Planus, *Arch Dermat & Syph* **7** 625 (May) 1923. (e) Hallopeau, H., and Lemerre, G. Sur un lichen plan aigu avec production de bulles et desquamation furfuracée, *Bull Soc franç de dermat et syph* **12** 77, 1901. (f) Grunenberg, T. Lichen ruber pemphigoides bzw bullösus und Blasenbildung bei Lichen ruber planus nach Arsen- und Germaninbehandlung, *Dermat Wchnschr* **109** 1239 (Oct 28) 1939. (g) Miller, J. W. A Case of Lichen Planus Bullosus, *J Cutan Dis* **29** 332 (July) 1911.

the bullous or vesicular eruption was present, with apparent improvement. In still other cases arsenic had been given after the bullae or vesicles had subsided with no recurrence of these lesions.

In the case herein reported, the first bullous outbreak was originally interpreted as a possible reaction to arsenic. However, in view of the recurrence of the bullous eruption after an interval of freedom from bullae during which time no arsenic was given, it seems more likely that the whole picture was that of lichen planus pemphigoides. At no time during either hospital admission was the urinary arsenic excretion above the levels of normal.

Although it seems unlikely that the bullous eruption was due to arsenic, such a possibility cannot be entirely ruled out since minute quantities of a drug may produce an eruption in a person hypersensitive or allergic to that drug and since, even after cessation of new exposures to the specific allergen, an eruption due to drugs may remain and may continue to present new lesions for some time.¹⁰

Some authors¹¹ have expressed the opinion that trauma resulting from scratching was responsible for the formation of bullae or vesicles. Engman¹² reported a case in which vesicles could be produced by rubbing an itching area. If nonitching areas were traumatized no bullae appeared. Allen¹³ observed that in curetting lichen planus papules in 1 of his patients vesicles appeared in the lesions thus treated. Gruneberg¹⁴ also reported a case in which vesicles could be produced by trauma to the lichen planus papules. In other cases the patient had little or no itching, and still vesicles appeared.¹⁵ Certainly, itching and scratching are common in most cases of lichen planus, and yet vesicles and bullae are infrequently seen in this disease. In some cases,¹⁵ as in the case herein reported, no bullae appeared on the back. It might be surmised that pressure prevented vesicle formation, since bedridden patients are likely to lie on their backs much of the time.

As to the mechanism of the formation of bullae and vesicles, most observers have expressed the opinion that it might readily be explained by increase in size of the so-called Max Joseph's lacunas. These spaces

10 Sulzberger, M. B. *Dermatologic Allergy*, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 392.

11 Trautmann, G. *Zur Lehre des Lichen ruber pemphigoides*, *Dermat. Ztschr.* **13** 317 (May) 1906.

12 Engman, M. F. *Report of a Case of Bullous Lichen Planus*, *J. Cutan. Dis.* **22** 207 (May) 1904.

13 Allen, C. W. *Lichen Planus as a Vesicular or Bullous Disease*, *J. Cutan. & Genito-Urin. Dis.* **19** 475 (Sept.) 1901.

14 Leredde, M. *Le lichen plan a forme bulleuse*, *Ann. de dermat. et syph.* **6** 637, 1895. Tryb, A. *Lichen ruber pemphigoides*, *Dermat. Wchnschr.* **74** 563 (June) 1922.

15 Miller¹⁰ Trautmann¹¹

are subepidermic and are located in the lichen planus papule. This mechanism would not explain the occasional intraepidermic vesicle formation as described by Fordyce,¹⁶ Whitfield,⁸ Golay^{9c} and Ruete¹⁷ and as illustrated in the work by Percival, Drennan and Dodds.¹⁸ Examples of this phenomenon are present in the slide collection at the New York Skin and Cancer Unit. Enlargement of Max Joseph's lacunas would not explain the formation of vesicles and bullae on skin not involved with the typical changes of lichen planus. Attempts at explanation of this mechanism are many and varied, but few are in agreement with others.

The improvement of the eruption following administration of suramin sodium cannot be attributed with certainty to the effects of that drug. From all reports reviewed, bullous eruptions in lichen planus were generally self limited, therefore, the seeming benefit from any drug must be analyzed with objectivity and critique. However, Gruneberg^{9f} reported improvement in a case of lichen planus pemphigoides following the administration of "germannin," a German drug equivalent to the American drug, suramin sodium. Scheiber¹⁹ reported improvement in papular lichen planus following "germannin" therapy. In the case here reported, the improvement which followed suramin sodium administration was rapid and unequivocal.

From all clinical descriptions in the literature, truly bullous lichen planus or lichen planus pemphigoides seems to present a fairly characteristic clinical picture and seems to run a rather definite course. The bullous phase is preceded by an acute outbreak of widespread lichen planus, usually composed of individual scattered lesions and plaques of lichen planus papules. There may also be patches of erythema of varying size without distinct lichen planus papules. The patient may or may not have had previous attacks of lichen planus. The bullous eruption usually appears suddenly. From the first, the bullae are most numerous and are of greatest diameter on the extremities. The bullae are usually fairly thick walled and rupture with difficulty, leaving eroded bases which heal readily. The bullae usually contain clear fluid, but the fluid may be hemorrhagic or purulent. At times removal of the tops of the bullae reveals their contents to be coagulated, as in the present case. These bullae usually come in crops and are frequently preceded by severe itching of the involved areas. The lesions show a tendency to

16 Fordyce, J. A. The Lichen Group of Skin Diseases. A Histological Study, *J. Cutan. Dis.* **28** 56 (April) 1910.

17 Reute, A. E. Lichen ruber planus pemphigoides, *Dermat. Ztschr.* **53** 522 (April) 1928.

18 Percival, G. H., Drennan, A. M., and Dodds, T. C. Atlas of Histopathology of the Skin, Edinburgh, E. & S. Livingstone, Ltd., 1947, p. 97.

19 Scherber, G. Zur Behandlung verschiedener Formen von Lichen ruber planus mit Germanin, *Dermat. Wchnschr.* **98** 797 (June) 1934.

grouping Vesicular lesions have been reported in the mouth, the pharynx, the larynx and, in 2 cases, in the esophagus²⁰ All these sites appeared to be affected in the case here reported Bullae may appear on lichen planus lesions, on patches of erythema or on apparently normal skin The diameter may range from pea to egg size or larger Nikolsky's sign may be present or the diameter of the bullae may be observed to increase on pressure with the finger on the top of unbroken lesions The crops of vesicles and bullae gradually decrease in size, in number of component lesions and in frequency of appearance The lichen planus papules may show improvement before, concomitant with or following the improvement of the bullous lesions but abatement of each manifestation is not separated by a long time interval The bullous eruption may last from a few weeks to several months

Pigmentation frequently appears in areas of preexisting lichen planus It is usually brownish or sepia in hue In some cases discoid areas of relatively less pigmentation may appear where bullae have been, and these spots may be slightly elevated The skin usually eventually regains its normal color

Constitutional symptoms are often present Fever may vary from a low grade intermittent or remittent type to high remittent fever There is usually general malaise, poor appetite, some weight loss and weakness These symptoms are present only during the more active phase of the bullous eruption

In a few cases minor recurrences of the bullous eruption followed within a few months, but as a general rule these did not last more than two or three weeks No report was found of a severe and prolonged recurrence of the bullous eruption

The most frequently used internal medication was arsenic in various forms "Germanin"²¹ has been reported of value, and estrogenic hormone seemed beneficial in 1 case^{3c}

Reports of fatalities have been few Pringle (Crocker¹) reported a death in a person from a generalized exfoliative dermatitis which complicated acute bullous lichen planus Rona²¹ reported death from pneumonia of a patient with widespread lichen planus which displayed a few vesicular lesions

SUMMARY

A case of lichen planus pemphigoides is reported and the course and observations described in detail The common characteristics of this rare and severe variant of lichen planus are described and discussed together with a review of the observations in previously reported cases

20 Zugerma and Gross^{3c} Dubois-Havenith, M *Lichen planus de Wilson*, *Presse med belge* 46 179 (June) 1904

21 Rona, S *Weitere Beiträge zur Lehre des Lichen ruber*, *Monatsh f prakt Dermat* 8 245 (March) 1889

VITILIGO WITH RAISED BORDERS

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AND

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WE ARE reporting a case of vitiligo with raised borders because of its rarity and unknown pathogenesis

REPORT OF A CASE

A L,¹ a boy aged 12, was admitted for treatment at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb 25, 1946, presenting depigmented patches of two months' duration. He had scarlet fever, measles, chickenpox and mumps during early childhood and impetigo of the face and eyebrows at the age of 7. There was dry diffuse seborrhea of the scalp but no loss of hair. The patient was sensitive about the appearance of the white patches. There were no subjective symptoms. The lesions were not preceded by tingling or itchy sensations. His general health was unimpaired.

A white spot first appeared on the penis. A similar spot developed two weeks later on the forehead, after an interval of two weeks, spots appeared on the left eyebrow and right ankle and after a lapse of another month on the left frontal region at the hair margin. The first patch on the forehead appeared as a slightly raised angry-looking reddish spot the size of a large pea. The patient applied ointment of benzoic and salicylic acid for three weeks and later tincture of iodine without result. After a period of several weeks this spot enlarged by peripheral extension and was associated with central clearing.

Dermatologic Examination—The patient presented depigmented milky white patches on the forehead and outer side of the left eyebrow, left side of the neck, left shoulder, penis and right ankle. They varied in size from 1 to 3 cm. On the forehead were two different lesions. One was a pigmented nevus, surrounded by a zone of vitiliginous skin, situated just below the hair margin. The other was a patch of vitiligo with a raised border, below and to the left of the nevus. The pigmented nevus, present since birth, was oval shaped, dark brown, level with the surrounding skin, 2.5 by 1.5 cm, with a sharply defined paper white halo enclosing it, and measuring 0.5 cm in width. The vitiliginous patch with the raised border was perfectly round, 2.5 cm in diameter, completely and evenly encircled by a threadlike border, the inner surface of which was white while the outer was of the same darker color as its neighboring integument. The pigmented nevus with its halo was isolated when first seen on February 25, but the lower margin of the halo had fused with the upper margin of the vitiliginous spot beneath it when examined on June 4 (fig 1). On the outer half of the left eyebrow, located horizontally, was an oval spot, also with a raised edge, 1.25 by 2.25 cm. There were

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¹ The patient was presented before the New York Dermatological Society, March 26, 1946 by Dr Fred Wise, on whose service the patient was treated

a few white hairs on the outer half of the left eyebrow and vitiliginous patches without raised borders, the size of a pea to that of a finger nail, on the left side of the neck, inner surface of the left shoulder, corona and shaft of the penis and outer surface of the right ankle. The depigmented patches were not altered in texture and were not surrounded by hyperpigmented borders.

General Medical Examination—The patient appeared to be in good health. He measured 5 feet 3½ inches (158.75 cm) and weighed 97 pounds (44.1 Kg). Physical examination revealed no evidence of internal disorders. The thyroid was not palpably enlarged. The pupils were moderately dilated and reacted well to light and in accommodation. The heart sounds and lungs were normal. The liver and spleen were not enlarged. The knee jerks were normal.

Laboratory Data—The Wassermann and Kahn reactions were negative, and urine examination was normal. Blood examination showed a normal total carot-



Fig 1—Two vitiliginous patches with raised borders, one just below the pigmented nevus and the other on the left eyebrow, the outer half of which shows whitish hairs.

tenoid content of 60 units per hundred cubic centimeters (normal 50 to 100) and a lowered vitamin A content of 5 blue units per hundred cubic centimeters (normal 10 to 20), with the Carr-Price method.²

Histologic Observation—From a section taken from the lesion with the raised border on the left side of the forehead (fig 2), Dr. Charles F. Sims gave the diagnosis of "superficial exudative inflammatory process," with the following description: "The rete pegs for the most part were rather short and the papillary bodies broadened. The granular layer was intact throughout the section and composed of one to three layers of cells. The rete was rather thin, and at several parts basal cell liquefaction could be observed. At these points exocytosis were noted. In one

² Booher, L. E. Vitamin A in Health and Disease, in Wohl, M. G. Dietotherapy. Clinical Application of Modern Nutrition, Philadelphia, W. B. Saunders Company, 1945, p. 225.

portion of the section there was apparently a diminution or total absence of pigment. The vessels of the upper part of the corium were moderately dilated, particularly the capillaries in the papillary bodies. Some interstitial and parenchymatous edema of the collagen in the affected zones were noted.

Under high power magnification the following observations were made. The cells were composed for the most part of small round cells, wandering connective tissue cells and some scattered chromatophores. The reaction for the most part was perivascular, except for the areas aforementioned.

Treatment—One teaspoonful of granular brewer's yeast and 10 drops of dilute hydrochloric acid in a glass of water through a glass tube were ordered to be taken three times a day after meals. A mixture of 10 cc of lotio neocalaminae and 20 cc of lotio calaminae was prescribed to be used as a cover.

The patient was reexamined on June 4. At that time the raised borders of the vitiliginous patches had almost entirely regressed and were only faintly perceptible. There were no changes in the tint of the depigmented patches. More white hairs were seen on the outer half of the left eyebrow.

Examination on October 31 showed that the pigment in the nevus had almost entirely disappeared.



Fig 2—Photomicrograph of the biopsy specimen taken from the raised border, showing the perivascular superficial exudative inflammatory process ($\times 78$)

COMMENT

Vitiliginous patches with raised borders are of rare occurrence. In review of the literature we found only 2 cases. A girl aged 10 years was presented before the Chicago Dermatological Society, October 21, 1936, by Becker and Obermayer³ as a case for diagnosis. She had oval depigmented plaques on various parts of the body. Those on the neck showed "a slightly elevated threadlike border." Becker, in the discussion, stated, "As to the peculiar threadlike inflammatory border, we have searched through the literature and have found only 1 case in which the condition may be identical with that of this patient⁴. Some of

³ Becker, S. W., and Obermayer, M. E. A Case for Diagnosis (Vitiligo? Atrophic Lichen Planus?), *Arch. Dermat. & Syph.* **36**: 216 (July) 1937.

⁴ Habermann, R. Paratypische Pigment-Anomalien, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1933, vol. 4, pt. 2.

the men who have written about vitiligo, Gans, for instance, stated that there may be a subthreshold inflammatory reaction Gougerot said that it is always due to subinflammatory reaction, but it may be that in this child there is sufficient inflammatory reaction to produce a real border " The patient was again presented on April 21, 1937,⁵ before the aforementioned society, as a definite case of vitiligo

The patient referred to in Jadassohn's Handbuch was that of Freudenthal,⁶ who described a case of vitiligo associated with an elevated red border in a patient with "lues II and III," under the title "luetic leukomelanoderma in the form of a pseudoviteligo" The patient had seropositive syphilis On the right lower quadrant of the abdomen were two depigmented patches, one discoid, with a diameter of about 2 inches (5 cm), and the other ovoid, about 6 by 2 inches (15 by 5 cm) These depigmented areas showed sharply defined slightly elevated red borders They appeared shortly after the regression *in situ* of an erythematous serpiginous late syphilitic exanthem

A case of leukoderma^{6a} with inflammatory borders was presented by one of us (F W) before the Manhattan Dermatologic Society on May 13, 1941⁷ The patient, a woman aged 47, had leukodermic patches on the wrists, forearms and front of the neck On the latter area the lesions were bordered by a "distinct red slightly raised finely scaled border, 2 to 3 mm in width" She had frequently been using ammonia and scouring powder in her work as chambermaid When the patient was seen two weeks later, the inflammatory borders had entirely regressed

The pigmented nevus and its halo (fig 1) could properly be called leukoderma acquisitum centrifugum, since it has in common with the condition described by Sutton,⁸ and more so with the verrucous and hairy nevi surrounded by achromic zones reported by Stokes,⁹ a whitish oval spot enclosing a nucleus-like primary lesion However, in the light of the newer conception that the depigmented zone and its central lesion in some cases of Sutton's disease are component parts of a whole nevus,¹⁰ at least the first word in the title leukoderma acquisitum centrifugum is

5 Becker, S W, and Obermayer, M E Vitiligo, Arch Dermat & Syph **37** 99 (Jan) 1938

6 Freudenthal, W Lüsche Leukomelanoderme unter dem Bilde einer Pseudoviteligo, Arch f Dermat u Syph **156** 142, 1928

6a Leukoderma is here interpreted as secondary depigmentation and vitiligo as a primary loss of pigment

7 Wise, F Leukoderma with Inflammatory Border, Arch Dermat & Syph **45** 218 (Jan) 1942

8 Sutton, R L An Unusual Variety of Vitiligo (Leukoderma Acquisitum Centrifugum), J Cutan & Ven Dis **34** 797 (Nov) 1916

9 Stokes, J H Leukoderma Acquisitum Centrifugum (Sutton), Arch Dermat & Syph **7** 611 (May) 1923

10 Feldman, S, and Lashinsky, I M Halo Nevus, Leukoderma Centrifugum Acquisitum (Sutton), Leukopigmentary Nevus, Arch Dermat & Syph **34** 590 (Oct) 1936

erroneous since in leukoderma no changes are normally found except depigmentation. Halo nevus, suggested by Feldman and Lashinsky¹¹ or, perhaps, nimbus nevus, would, therefore, be a more suitable term.

The superficial exudative perivascular inflammatory process with the round cell infiltration would indicate the possibility of a toxic cause for the vitiliginous patches of our patient. This conception is strengthened by the lowered vitamin A content of 5 blue units per hundred cubic centimeters of blood (normal 10 to 20), as a deficiency in vitamin A may lower the natural resistance to various bacterial infections, possibly due, as expressed by Kolmer,¹² to "some defect in the efficient functioning of the reticuloendothelial system."

The treatment was that described by Hathaway,¹³ who treated 14 patients with vitiligo with 2 capsules of vitamin B complex fortified with nicotinic acid, thiamine hydrochloride and riboflavin and 10 minims (0.62 cc) of dilute hydrochloric acid after meals. In 9 patients who cooperated, the disease cleared up in 7 and improved in 2. These patients continued the medication for one to two years, with half the dose after the patches assumed the coloration of the surrounding skin.

Hathaway raised the question as to which component or components in the vitamin B complex may be responsible for the good results achieved. This unknown factor may be para-aminobenzoic acid, as Sieve¹⁴ reported the gradual return of pigmentation in cases of vitiligo with 100 mg tablets of this acid administered three times a day.

SUMMARY

A patient is herein presented with vitiliginous patches, two of which, on the forehead, had distinct raised borders. Only 2 such cases have thus far been reported in literature, 1 by Becker and Obermayer and 1 by one of us (F. W.). The case reported by Freudenthal was in a patient with tertiary syphilis.

The title halo nevus rather than leukoderma acquisitum centrifugum is more suitable for the pigmented nevus and its whitish halo in our patient and for all achromic zones containing a central nevus.

The perivascular round cell infiltration and the lowered vitamin A content in the blood would suggest that the causative factor in our case may be of a toxic nature. The treatment with vitamin B complex and dilute hydrochloric acid was prescribed according to the method reported by Hathaway.

11 Feldman and Lashinsky,¹⁰ p. 594

12 Kolmer, J. A. Nutrition in Relation to Infection and Immunity, in Wohl, M. G. Dietotherapy. Clinical Application of Modern Nutrition, Philadelphia, W. B. Saunders Company, 1945, p. 521

13 Hathaway, J. C. Vitamin B Complex for Vitiligo, Arch. Dermat. & Syph. 52: 117 (Aug.) 1945

14 Sieve, B. F. Effects of a New B Complex Factor on Pigmentation and Fertility. South. Med. & Surg. 104: 135 (March) 1942

PSORIATIC ERYTHRODERMA, EPITHELIOMATOUS CHANGES AND WARTLIKE GROWTHS

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AND

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IN 1925 Levin¹ recorded a unique instance of universal psoriasis complicated by tumor-like formations. At that time he stated the belief that these lesions resembled those described by Unna² (1890) as parakeratosis scutularis and by Weiss³ (1912) as parakeratosis ostracea. The outstanding clinical feature was the presence of verrucous excrescences, varying in size from that of a lentil to that of a quarter, some pale and others pink, and occurring chiefly on the lower limbs in irregular distribution. The pathologic features reported by Levin were those of typical psoriasis, accompanied with pronounced acanthosis of a degree sufficient to explain the warty clinical appearance. The tumor-like aspect was attributed by him to a combination of swelling of the fibrous tissue, intense acanthosis and cellular infiltration in the cutis. Arsenic was eliminated as a possible cause. In 1939 Levin presented this patient again⁴. In the interim, since 1937, these nodules had increased in size and several had undergone subsequent ulceration. Levin reported that in 1934 a biopsy specimen of one of the ulcerated lesions had revealed evidence of epithelioma, probably squamous in type (pearl formation). On the other hand, a biopsy specimen removed in 1939 revealed changes that were consistent with the diagnosis of psoriasis verrucosa. In the discussion of this case Peck stated that there were at least two other biopsies which had shown only changes of typical psoriasis, one additional biopsy showing a fibroma in the cutis and still another revealing alterations that

From the Dermatologic Service of the Montefiore Hospital for Chronic Diseases, New York

1 Levin, O L. Universal Psoriasis Complicated by Tumor-Like Formations, *Arch Dermat & Syph* **12** 360 (Sept) 1925

2 Unna, P G. Parakeratosis Scutularis, in Unna, P G, Morris M Duhring, L A, and Leloir, H. *Atlas von seltener Hautkrankheiten*, Hamburg, L Voss, 1890

3 Weiss, L. Parakeratosis Ostracea (Scutularis), *I A M A* **59** 343 (Aug 3) 1912

4 Levin, O L. Erythroderma Psoriaticum with Tumor Growths (Epitheliomatous Changes), *Arch Dermat & Syph* **41** 1180 (June) 1940.

were strongly suggestive of epithelioma. Nevertheless, Peck doubted that this patient had had a true epithelioma. However, the title of this presentation indicated that Levin regarded the epitheliomatous changes as an important part of the clinical picture.

It is apparent that the views on this subject are discordant and need further clarification. For the purpose of establishing this peculiar syndrome on a clinicopathologic basis, we are reporting additional data on the subsequent course of Levin's case as well as another striking example of this entity.

REPORT OF A CASE

I G, a man aged 22, was admitted to Montefiore Hospital Dec 12, 1944, with a widespread eruption that had first appeared at the age of 2½ years in the form of red scaly areas on the tibias. At the age of 7, similar lesions were observed on the forearms, and these soon coalesced into large patches. At about this time he received medication in the form of drops by mouth, but this was stopped at the end of a week because he complained of frequent urination. Following this, he received roentgen rays to various parts of the body for a period of several months. Some time later, ultraviolet irradiation was used. In 1933 he was observed at another hospital, where a diagnosis of psoriasis was made. Subsequently, the skin on the dorsa of the hands was affected, and still later patches appeared on the trunk. About five years before our observation the skin of the entire body, for no apparent reason, became red, dry and scaly, and, at about this time, the joints of the ankles and knees became red, swollen and painful. Several months later, the articulations of the right hand were similarly affected. Although there were periods of improvement, at no time did the skin or joints return to a normal state, nor was there ever evidence of a pustular or moist component in the cutaneous lesions. Shortly before admission, the joints of the left hand became red, swollen and painful. The past history and the family history were noncontributory.

Physical examination revealed a universal, nonpruritic, erythematous and scaly eruption. On the scalp the scales were dry and silvery white. On the body the erythema was bright red, such as is commonly seen in the psoriatic process. The dorsa of the feet were diffusely covered by a similar eruption, with a sharp margin about ¼ inch (about 1.9 cm) from the soles. There were discrete areas of eruption on the soles, these patches having distinctly psoriatic attributes. There were subungual hyperkeratoses of the finger nails. In addition, the skin of the legs and left forearm showed scattered irregularly elevated rough wartlike excrescences, varying in size from that of a pinhead to that of a small pea. In particular, there were two larger wartlike lesions, one on the left forearm and the other on the left knee. The palms and soles were free of any changes that might be considered as arsenical keratoses. There was also deforming arthritis, which involved chiefly the hands and feet and to a lesser degree the knees and cervical part of the spine.

The laboratory studies (such as blood cell count, serologic test, urinalysis, determination of blood calcium and cholesterol, serum sodium and potassium, serum albumin and globulin, glucose tolerance test and basal metabolic rate) revealed no significant abnormalities. Erythrocyte sedimentation rate was somewhat more rapid than normal (21 mm in one hour). Vitamin C saturation test showed some retention, the significance of which is unclear. At the Presbyterian Hospital (1944) an arsenic determination revealed a value of 0.07 mg per hundred grams of dried blood, a

result considered to be within the limits of normal. Our laboratories (1946) found only a faint trace of arsenic in a twenty-four specimen of urine, a result likewise regarded as essentially normal. Roentgenograms of the various affected joints showed abnormalities which were consistent with the diagnosis of rheumatoid arthritis.

The nature of the eruption, the peculiar bright red color, the circumscription of the rash at the lower margins of the feet, the circumscribed red scaly patches on the soles, the striking subungual hyperkeratoses of the finger nails and the type of arthropathy in this young person were changes that were consistent with the diagnosis of psoriatic arthropathy and psoriatic erythroderma. Moreover, observers

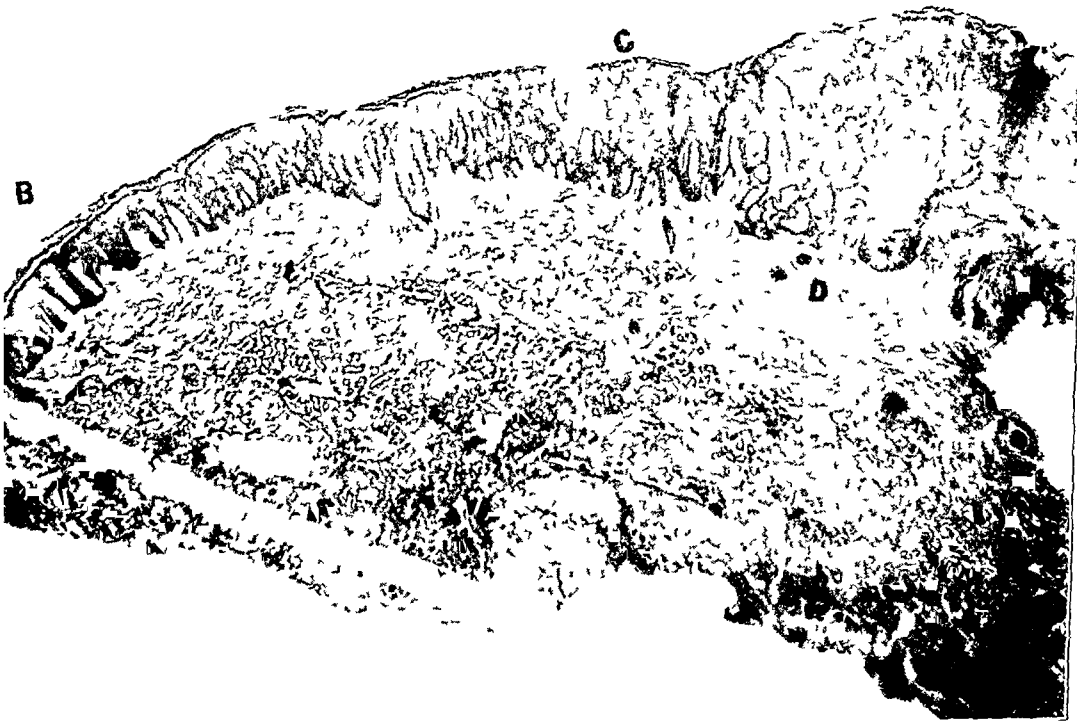


Fig 1—In the same section are seen an area of psoriasis (B), an intermediate zone with irregular and intense acanthosis, with numerous daughter peglike processes (C), and an area of basal cell epithelioma (D) ($\times 10$)

who had seen the patient previously in the earlier stages of the disease had unanimously agreed that the eruption was a typical example of psoriasis.

The main interest in this case was centered about the peculiar warty formations on the left forearm and lower limbs, particularly since one of us had observed similar lesions in the case recorded by Levin. For this reason, the histologic studies made on these lesions will be described in detail.

Histopathologic Studies—Biopsy A. On the extensor aspect of the left forearm, several inches above the wrist, there was a round grayish yellow wartlike lesion, about 5 mm in diameter and elevated about 2 mm. This lesion had been first noted by the patient a few months before the present admission, and it had not grown appreciably within the period of our observation of over one year nor had

there ever been any evidence of ulceration at any time. The growth was completely excised July 23, 1946. The psoriatic eruption on this limb had been present continuously for over ten years.

Microscopic study disclosed that the lesion was composed of three relatively distinct portions: (1) an area of typical psoriasis, (2) an intermediate zone and (3) an area showing alterations of a neoplastic nature, arising gradually from the preceding portion (fig 1). In the part of the section showing the changes of psoriasis (fig 2) there was acanthosis, as indicated by long fairly regular pegs. The overlying epidermis revealed many scattered areas of parakeratosis which were commonly seen in relation to the thinned out suprapapillary plates. The malpighian

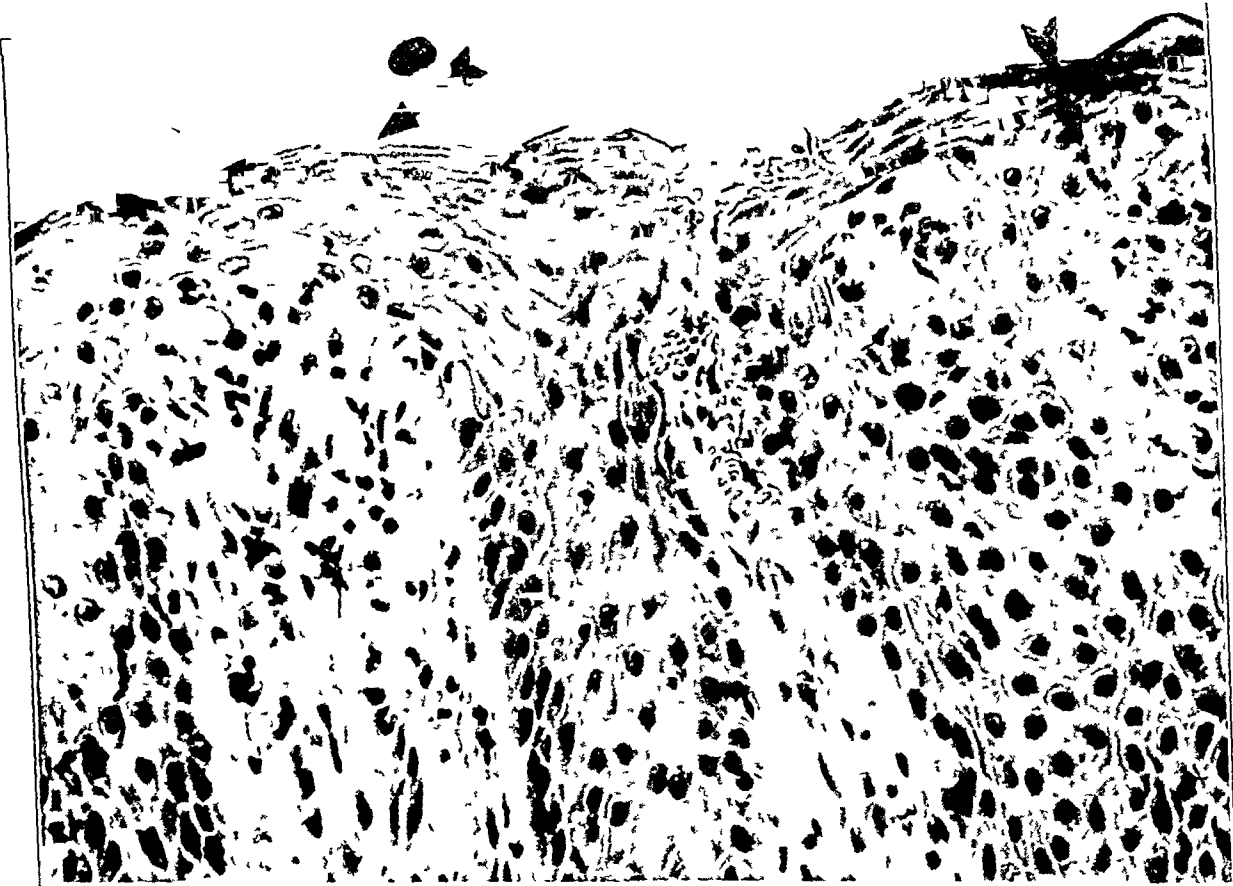


Fig 2—High power of area B in figure 1. Section shows the features of psoriasis. The black arrow on the left side of the photograph points to a zone of parakeratosis and thinned out suprapapillary plate. The black arrow on the opposite side points to a wandering cell in a channel-like space (description in text) ($\times 200$).

layer was slightly edematous and revealed a moderate degree of intracellular and intercellular edema. Scattered throughout this area, particularly in the upper portion, were longitudinal narrow spaces containing deformed white blood cells in a channel-like distribution; these cells resembled sometimes polymorphonuclear leukocytes and at other times deformed mononuclear cells. No definite microabscesses were seen. The papillae were, for the most part, regularly elongated and congested and revealed a mild cellular infiltrate of nonspecific type. As one proceeded toward the neoplasm, the rete pegs became more and more elongated and irregularly distributed, with more and more daughter peglike processes. In the intermediate zone (fig 3) the peglike processes seemed normal in appearance, except

that the corresponding subpapillary areas were sites of a relatively pronounced reactive inflammation. A point was reached where the daughter pegs began to take on the appearance of a basal cell epithelioma, as indicated by the collections of basal cells of hyperchromatic character. Finally, at one point (fig 4)



Fig 3—High power of area C in figure 1. The irregular acanthosis with the daughter processes is seen. At 4, the latter are seen as well as the diffuse reactive inflammation. The arrow points to beginning basal cell epithelioma ($\times 30$).

there was an area in which the basal cell epithelioma seemed to be breaking through the basement membrane, and here the cells seemed to have assumed a more transitional character. The reactive inflammatory process was most pro-

nounced in that portion of the section which was of neoplastic nature. The epithelioma and its corresponding inflammatory zone did not extend below the middle portion of the cutis.

Biopsy B. The second growth (fig 5), which was present on the front of the left knee, was similar in appearance to the one previously described, except that



Fig 4—High power of area D in figure 1. An area of basal cell epithelioma. The arrow points to a portion of neoplasm that seems to be breaking through the basement membrane ($\times 30$).

it was slightly larger (6 mm in diameter). The patient had first noted this lesion about two years before admission. This growth was excised November 7. The eruption of psoriasis on this limb had been present more than fifteen years.

Microscopic study revealed the characteristic changes of psoriasis. To one side of the center of the section, the papillary pegs were elongated and irregular, and in one portion of the middle part of the cutis there were two or three collections of hyperchromatic cells, which, in the opinion of Dr. W. Sachs, constituted probable evidence of early basal cell epithelioma. Adjacent to this area there was a fairly



Fig. 5—The arrow points to the growth on the area of the left knee (histopathologic studies, biopsy B, in text). In the area below the growth, there are irregular excrescences in a mild form.

well circumscribed zone in the cutis, containing many young blood vessels with scattered fibroblasts and intertwining masses of collagenous tissue. This appearance, which at first seemed to resemble that of a fibroma, was subsequently interpreted as that of granulation tissue with secondary fibrosis. In microscopic examination (magnification 10 times) the central elevation of the lesion was seen to be

due almost entirely to this mass of granulation tissue along with the area of irregular rete pegs

Biopsy C For purposes of comparison, a third biopsy specimen was taken from an area of uncomplicated psoriasis, situated on the lateral aspect of the left leg about $1\frac{1}{2}$ inches (about 3.8 cm) below the knee (December 24). Except for the absence of microabscesses, the section showed the characteristic features of psoriasis. The rete pegs were regularly and gracefully elongated, with a moderate amount of congestion and inflammatory reaction of nonspecific type in the papillary bodies. There was a moderate amount of intercellular and intracellular edema in the malpighian layer, and this was surmounted by a heavily parakeratotic zone. There was no evidence of a granular layer throughout this section.

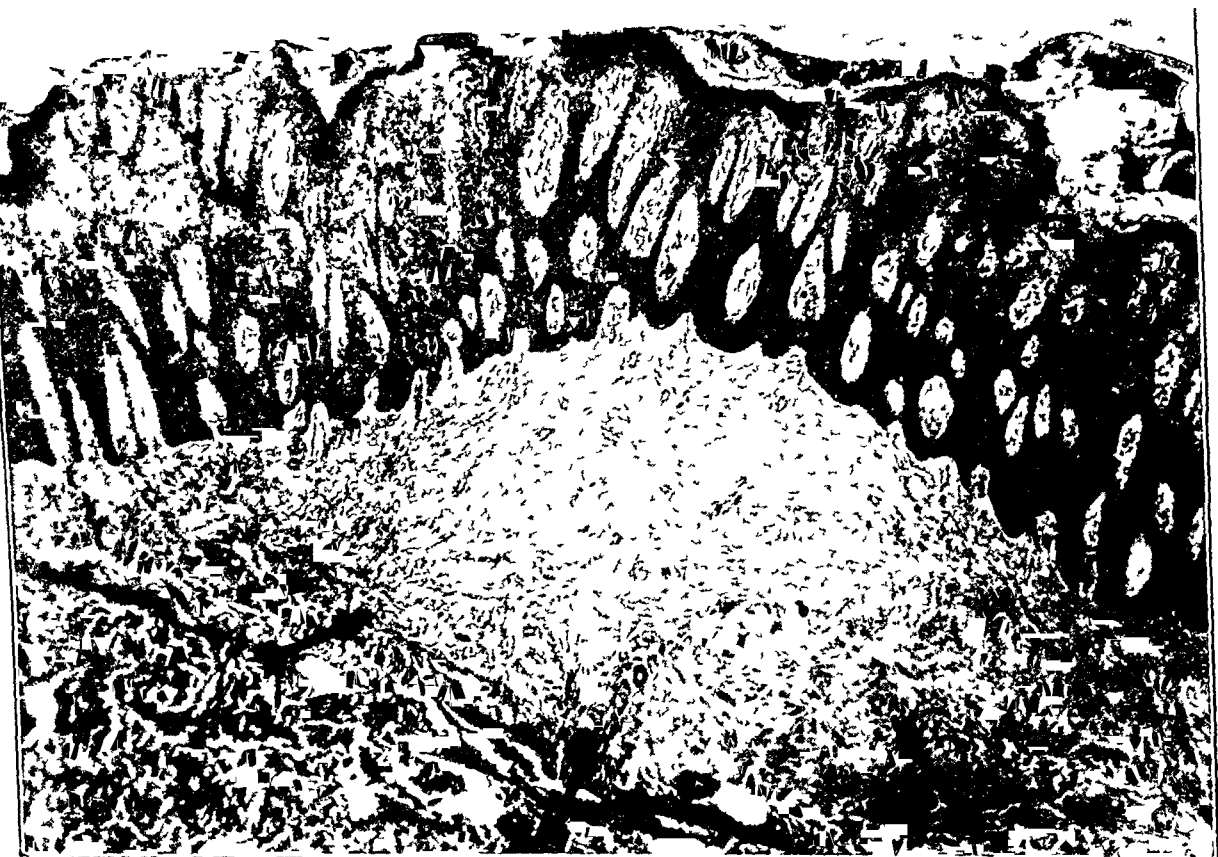


Fig 6—Irregular acanthosis over an area of fibrosis arising on the basis of granulation tissue. The fibrotic area is set off by arrows. The vascularity of this fairly well circumscribed lesion in the cutis may be noted. (See biopsy D and compare with biopsy B.)

Biopsy D The fourth biopsy specimen was taken from a wartlike lesion situated about $\frac{3}{4}$ inch (about 1.9 cm) from the site of biopsy C. The growth was 2 mm in diameter and elevated about 1 mm above the surface. In this section (fig 6) the features of psoriasis seemed to be masked somewhat by a pronounced irregularity in the rete pegs. In one portion of the section, near its center, there was a moderate inflammatory reaction in the subpapillary zone. Nearby, in the center of the lesion, there was an area containing collections of spindle cells and a considerable number of capillaries separated by irregular bands of fine and coarse collagenous fibers. This appearance resembled strikingly that already described in biopsy B, but differed only in its smaller size, its less circumscribed character.

and its more advanced stage of organization. In microscopic examination (magnification 10 times) the elevation in this warty growth was seen to be due to the presence of this inflammatory fibrotic area together with the overlying irregularly elongated rete pegs.

COMMENT

1 *Relation Between Psoriasis and Epithelioma*—Few observers have studied the possible relation between psoriasis and epithelioma and the views expressed on this point have been discordant. One of the most complete analyses of this subject is that given by Alexander, who collected 18 cases, mainly from the literature, in which this combination had been described. Alexander classified these cases into three groups: (a) 5 cases in which the epithelioma arose directly from arsenical keratoses found in patients afflicted with psoriasis, (b) 6 cases in which arsenic was thought to have caused a typical proliferation of psoriasis, without the intervention of arsenical keratoses, and (c) 7 probable instances in which isolated psoriatic lesions underwent direct carcinomatous change in the absence of such extraneous factors as arsenic. The last group was considered as analogous to carcinomas arising on areas of roentgen change, scars, lupus and the like.

It is not our intention to discuss all the possible examples in which combinations of psoriasis and epitheliomas of one type or another have been encountered. In many such instances the possibility of coincidence must be considered. In regard to Alexander's classification, we are unable to accept the sharp distinction between his first two groups on the basis of the cited case reports. There is evidence, for example, that the lesions in some of the cases in his second group were really epitheliomas occurring in areas of arsenical keratoses in unusual locations, a view that seems to be supported by the simultaneous occurrence in these cases of typical arsenical keratoses in the palms and soles. Possibly arsenic may cause atypical proliferation of epithelium in other dermatoses, and this has been postulated in the case of certain lesions, such as leukoplakia on a syphilitic background. However, Alexander's second group is based on data that are inadequate to substantiate this view, so far as psoriasis is concerned. We are also uncertain of whether all the cases grouped in Alexander's third class really belong there. Nevertheless, Alexander's report has the merit of attempting to separate examples of direct epitheliomatous changes in psoriatic lesions from the cancerous alterations caused essentially by such extraneous factors as the intake of arsenic and roentgen changes.

It is evident that, in order to establish the occurrence of direct epitheliomatous change in psoriasis, two possible complicating factors

5 Alexander, A. Carcinomentwicklung auf psoriatischer Basis, Arch f Dermat u Syph **129** 5, 1921 (extensive bibliography)

must be eliminated, namely, intake of arsenic and roentgen alterations. Arsenic is, of course, a factor that must always be considered in chronic dermatoses, since in such cases this medicament is apt to be given at one time or another. Whereas this is less likely to be true today, it was certainly a common occurrence a few generations ago when most epitheliomas in patients with psoriasis arose on the basis of arsenical keratoses. In Levin's case the patient did not receive arsenic in any form⁶. Our patient took drops about twelve years before observation, but this medicament, which was probably a preparation of arsenic, was discontinued after a week because of unpleasant side effects. It seems most unlikely that this small amount of arsenic can be implicated in the presenting epitheliomatous changes. In 1944 and 1946 arsenic determinations of the blood and urine, respectively, gave results within the limits of normal. Whereas this does not exclude the possibility of previous ingestion of arsenic, these data eliminate, at least, the possibility of continued absorption of large amounts of arsenic, either from ingestion or from exposure. As far as roentgen irradiation is concerned, Levin's case may have received radiation therapy many years ago, whereas our patient received a moderate amount of roentgen irradiation. However, neither in Levin's case nor in our own could evidence be found that these peculiar wartlike lesions arose on the basis of prior roentgen change. Clinically there was no evidence of radiodermatitis in the immediate neighborhood of these lesions, and this could be further substantiated in both instances by the absence of roentgen alterations in the various biopsy specimens taken.

We believe, therefore, that in both Levin's case and in our own, the factors of arsenic and roentgen change can be eliminated with reasonable certainty as cause of the epitheliomatous alterations. The evidence favors the view that in certain instances of psoriatic erythroderma primary epitheliomatous changes may occur in such altered skin.

2 Nature of the Wartlike Lesions In studying our material we found that there were essentially two types of pathologic alterations in the wartlike lesions observed in our case. (a) The first type was exemplified by the changes described in biopsy A. This disclosed a zone of basal cell epithelioma in juxtaposition to an area in which there was pronounced and irregular acanthosis. (b) The second type was illustrated by the observations in biopsies B and D. Here the wartlike appearances were created by the combination of irregular acanthosis and an area of granulation tissue going on to fibrosis. In Levin's patient one of the biopsies showed what was considered to be

⁶ Levin, O. L. Personal communication to the authors.

a fibroma. This is of interest because in our case the fibrotic granulation tissue was diagnosed at first as fibroma, an opinion which was revised when similar alterations were found in a second biopsy specimen from an area nearby. We feel that the report of fibroma in

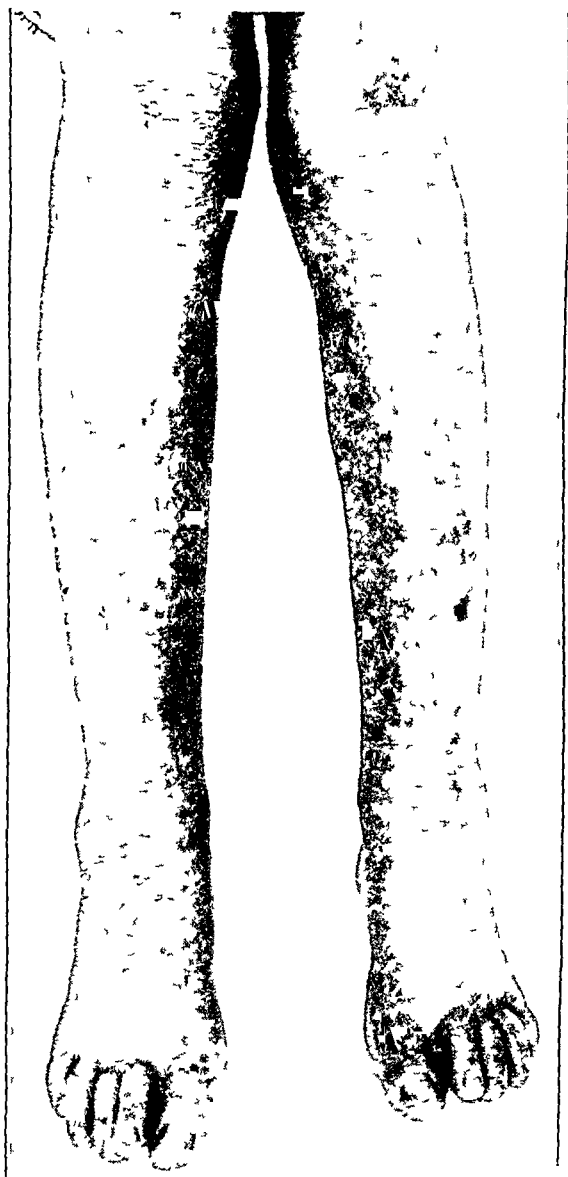


Fig. 7—Wartlike lesions on the legs of Levin's patient. These excrescences are in an early stage.

Levin's case should be reconsidered in the light of the observations that we have reported.

The common denominator of the three biopsies, A, B and D, was the presence of intense and irregular acanthosis. In biopsy A this

irregular acanthotic zone lay next to that area which was undergoing the changes of basal cell epithelioma. It is of interest that at one point of the section the basal cell epithelioma seemed to have penetrated the basement membrane. In Levin's case the pathologic diagnoses fluctuated between epithelioma and psoriasis verrucosa, whereas one sec-



Fig 8—The appearances on the legs of Levin's patient in a later stage. The small excrescences have now become large wartlike growths.

tion, as stated previously, showed a "fibroma" in the cutis. It is important, therefore, to report that in Levin's patient other lesions of squamous cell carcinoma developed, with metastases ending in death. On the other hand, our patient is a young person who has had the wartlike lesions only a few years, and we are therefore, in all likelihood observing early changes. We believe that the presence of pro-

nounced irregular acanthosis is probably a forerunner of epitheliomatous alterations in the future. Whether these will turn out to be purely basal cell or squamous cell epithelioma, we do not know.

3 *Clinicopathologic Features of the Syndrome*—The clinicopathologic features exhibited in our case were essentially the counterpart of those shown by Levin's patient. These 2 instances of psoriatic erythroderma illustrate the developmental phases of the peculiar wartlike lesions observed in such cases (figs 5, 7 and 8).

(a) *Clinical Features* The wartlike growths have been encountered in young persons (our patient was 19 years old at the time of observation) who have been afflicted with extensive psoriasis for many years. At onset these lesions vary in size from that of a pinhead to that of a pea. They are a dirty grayish yellow, are elevated only a few millimeters and present a rough surface fading gradually into what seems to be ordinary psoriatic skin. Their sites of predilection are the legs, where they are irregularly distributed. On palpation there is imparted the feeling of multiple uneven excrescences. These lesions may be seen as more or less discrete growths on other parts of the body, such as the forearms and face. In the latter situation the growths may be smoother to the touch, possibly because of rubbing incidental to washing the face. At their onset the growths are non-ulcerated and are apt to remain in this state for many years. They arise insidiously and grow gradually to form more elevated rough irregular plaques of variable size, some attaining the diameter of a dime, with irregular and uneven borders. After a variable period, usually measured in years, ulceration occurs in occasional lesions. Such ulceration seems to portend the occurrence of malignant change, probably squamous cell in type, as in Levin's case. It should be stressed, however, that epitheliomatous alterations may be encountered in nonulcerated growths, as in our case (basal cell epithelioma). Judging on the basis of Levin's case, the clinical course may be terminated by death because of metastases from one or more foci of squamous cell carcinoma, and, as the changes seem severest on the lower limbs, the inguinal glands are apt to be the first obvious site of a metastatic deposit. It is probable that various types and stages of epitheliomatous alteration may be seen in the later course of these cases.

Arsenic and roentgen effects can be eliminated with reasonable certainty as causative agents, the former on the basis of the clinical and laboratory observations, and the latter on the basis of the clinical features and the absence of roentgen changes in the histologic pictures.

(b) *Pathologic Features* The various biopsies made in Levin's case showed at different times changes classified as psoriasis verrucosa.

squamous cell cancer and fibroma. Our studies revealed that these wartlike growths could be classified in at least two categories: (1) intense and irregular acanthosis shading over into basal cell epithelioma (biopsy A) and (2) intense and irregular acanthosis overlying or in relation to granulation tissue undergoing fibrosis (biopsies B and D).

SUMMARY AND CONCLUSIONS

It appears that there is a definite syndrome in which long-lasting psoriatic erythroderma is accompanied subsequently with the appearance of nonulcerated wartlike growths on various parts of the body, especially the legs. These wartlike excrescences, which may or may not be associated with peculiar fibrotic changes in the cutis, are probably forerunners of epitheliomatous changes of various types. In their future course some of these lesions may ulcerate. Thus far, squamous cell epithelioma and an active type of basal cell epithelioma have been encountered, the latter in a nonulcerated growth. Whether chronic erythrodermas, other than the psoriatic type, are capable of giving rise to these peculiar wartlike lesions is a matter which requires further observations.

Dr. H. Zimmerman, Pathologist to the Montefiore Hospital, assisted with suggestions and criticisms.

OSTEOMA CUTIS

Report of a Case

MORRIS LEIDER, M D
BROOKLYN

OSSIFYING processes in the skin, either primary (neoplasia) or secondary (metaplasia), are rare occurrences. The discovery of bone formation in the skin is even rarer than its occurrence, and, consequently, reports of the phenomenon are rarest of all. Ossification in other extraskkeletal sites, aside from in the skin, is not too uncommon. Year after year there are several reports of bone deposit in organs like the kidneys and musculature. Prior to 1928 Hopkins¹ could find only about 5 cases, beginning with Virchow's case and including his own, of osteomas in the skin. Since then, i e., in the past twenty years, I have been able to discover only seven more reports of the condition.² There must be a few cases that have not been recorded in the periodical literature, like that of Andrews, who in his textbook³ cited an instance in which he was able to demonstrate the deposits of bone in the skin in roentgenograms made on dental film. In this dozen or so of cases some osteomas were secondary to preexisting lesions, like nevi, epitheliomas, scars and chronic inflammatory dermatoses, others were primary, i e., arising in apparently normal loci.

The case herein reported is nearly an exact replica of Hopkins' case¹ and both are unique in the number of osteomas recovered, their localiza-

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, of the New York Post-Graduate Medical School and Hospital (Dr Marion B Sulzberger, Director)

1 Hopkins, J G. Multiple Miliary Osteomas of the Skin. Report of a Case, Arch Dermat & Syph **18** 706 (Nov) 1928

2 (a) Dietrick, C. Osteomatosis Cutis, Arch Dermat & Syph **41** 562 (March) 1940. (b) Pirila, P. Genuine Cutaneous Osteoma. Case Report, Acta dermat-venereol **22** 360, 1941. (c) Higuti, K., and Mitumoto, S. Formation of Bone in the Skin (Osteoidoma Cutis). Two Cases, Hihū-to-Hitunyo (Abstr Sect) **9** 12 (April) 1941. (d) Lilga, H V., and Burns, D C. Osteomatosis Cutis. Report of a Case, Arch Dermat & Syph **46** 872 (Dec) 1942. (e) Mercadal Peyri, J., and Trallero Felez, J. Primary Subcutaneous Osteoma, Acta dermo-sif **35** 280 (Dec) 1943. (f) Vero, F., Machacek, G F., and Bartlett, F H. Disseminated Congenital Osteomas of the Skin with Subsequent Development of Myositis Ossificans. Case in an Infant, J A M A **129** 728 (Nov 10) 1945. (g) Costello, M. Metaplasia of Bone. Report of a Case, Arch Dermat & Syph **56** 536 (Oct) 1947.

3 Andrews, G C. Diseases of the Skin for Practitioners and Students, ed 3, Philadelphia, W B Saunders Company, 1946

tion and distribution in the face, their size and in several other respects relative to comparable data of the other cases. The table is a summary

Comparative Data in Two Cases of Osteoma Cutis

Data	Hopkins' Case	Case Described Herein
Age (yr)	44	34
Dermatologic history	Aene of 10 years' duration, onset at 30 years, comedos, papules, pustules, scars	Aene of 21 years' duration, onset at 13 years, comedos, papules, pustules, scars
Previous dermatologic treatment	Roentgen rays, vaccines, diet, topical remedies	Roentgen rays, vaccines, ultraviolet rays, diet, topical remedies
General medical history	"Many indefinite conditions, nature of which could not be determined"	Many indefinite conditions, nature of which are indeterminable by extensive medical work up
General condition	Essentially normal	Essentially normal
Psychiatric opinion	"Somewhat neurotic"	Decidedly neurotic
Laboratory observations	Blood cell count r b c 4,460,000, w b c 5,600, normal differential count, normal urine, blood chemistry (mg /100 cc) calcium 10.8, sugar 107.1, urea nitrogen 13.01, chlorides 495, cholesterol 250, phosphates not done, basal metabolic rate —19 per cent	Blood cell count r b c 4,410,000, w b c 6,800, normal differential count, normal urine, blood chemistry (mg /100 cc) calcium 11.8 (normal 9.6-11), sugar 85 (normal 80-120), urea nitrogen 14 (normal 10-15), chlorides 445 (normal 450-500), cholesterol 135 (normal 160-230), phosphates specimen hemolyzed 3.54, basal metabolic rate —16 per cent (1941), —10 per cent (1947)
Size of recovered osteomas	0.52 mm	0.515 mm
No. of recovered osteomas	30-50	12
Roentgen observations of soft parts	Not made	Multiple minute soft tissue calcific deposits in the skin of the chin, around the nose and brow (Dr Wm H Meyer)
Cell structure of specimen	Lamellated in concentric rings, numerous lacunae, most of which contained stainable nuclei, one or two Haversian canals were seen containing small vessels, specimen in situ	Concentric arrangement of structure showed numerous lacunae containing stained nuclei which gave the impression of being those of osteoblasts, specimen not in situ, this appearance occurs whether or not the specimens are in situ (Dr M N Richter)
Microchemical qualitative analysis	Calcium, phosphates, carbonates	Calcium, phosphates, carbonates, trace of protein, no silica

of the relevant and comparative data of both cases. Moreover, comparison of the photographs herein printed with those in Hopkins' article and with those of other cases shows further near-perfect similarity

between Hopkins' case and my own and the differences between these 2 cases and the others

REPORT OF A CASE

G S, a white woman aged 34, a stenographer, has been under continuous observation and treatment at the New York Skin and Cancer Unit and in the general medical and surgical services of the New York Post-Graduate Medical School and Hospital for the past seven years. Prior to that she was registered in the Stuyvesant Square Hospital Skin Clinic, in 1927, with the diagnosis of *acne vulgaris*. During the period of recent history her complaints had ranged through



Fig 1—Clinical aspect of the patient

many organs and systems, and if not yet quite all, then there is more to come. As a consequence, this patient's chart is thick with "work up." The results of these extensive clinical and laboratory examinations may be summed up with matching brevity—essentially normal except for the skin and the psyche. Literally, the dentist, proctologist, internist, surgeon, radiologist and clinical pathologist have not been able to reveal or establish any significant deviation from the normal. Only the dermatologist and the psychiatrist have found faults.

The dermatologic complaints involve the skin of the face. A history of acne goes back twenty-one years (to age 13). By the time I received the case the chief

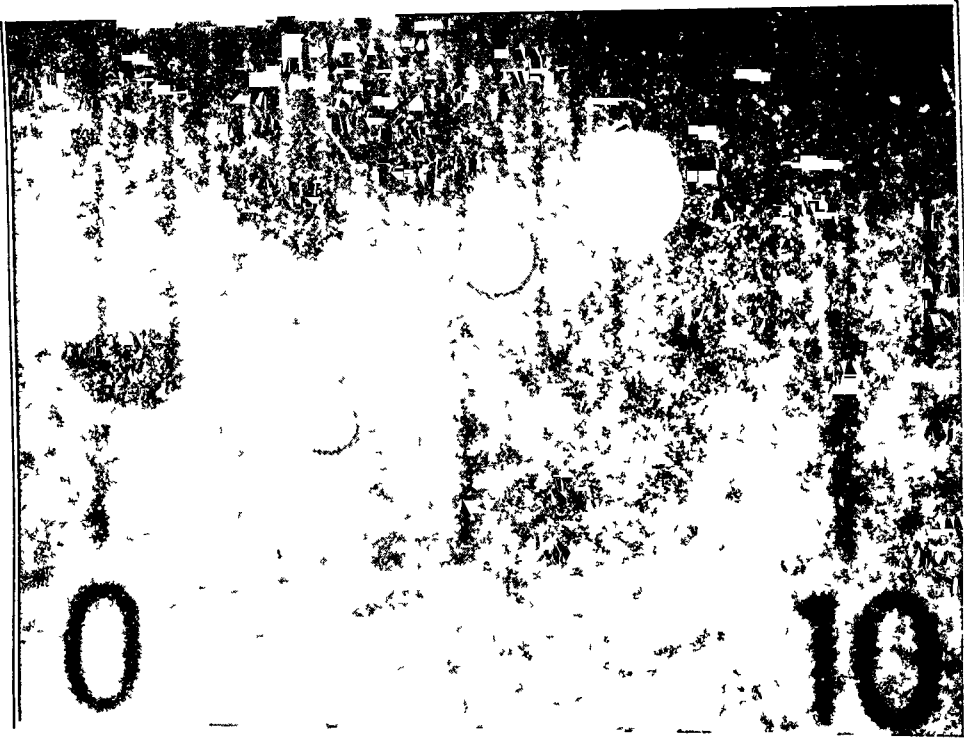


Fig 2—Gross appearance, showing size of osteomas ($\times 83$) against a millimeter scale

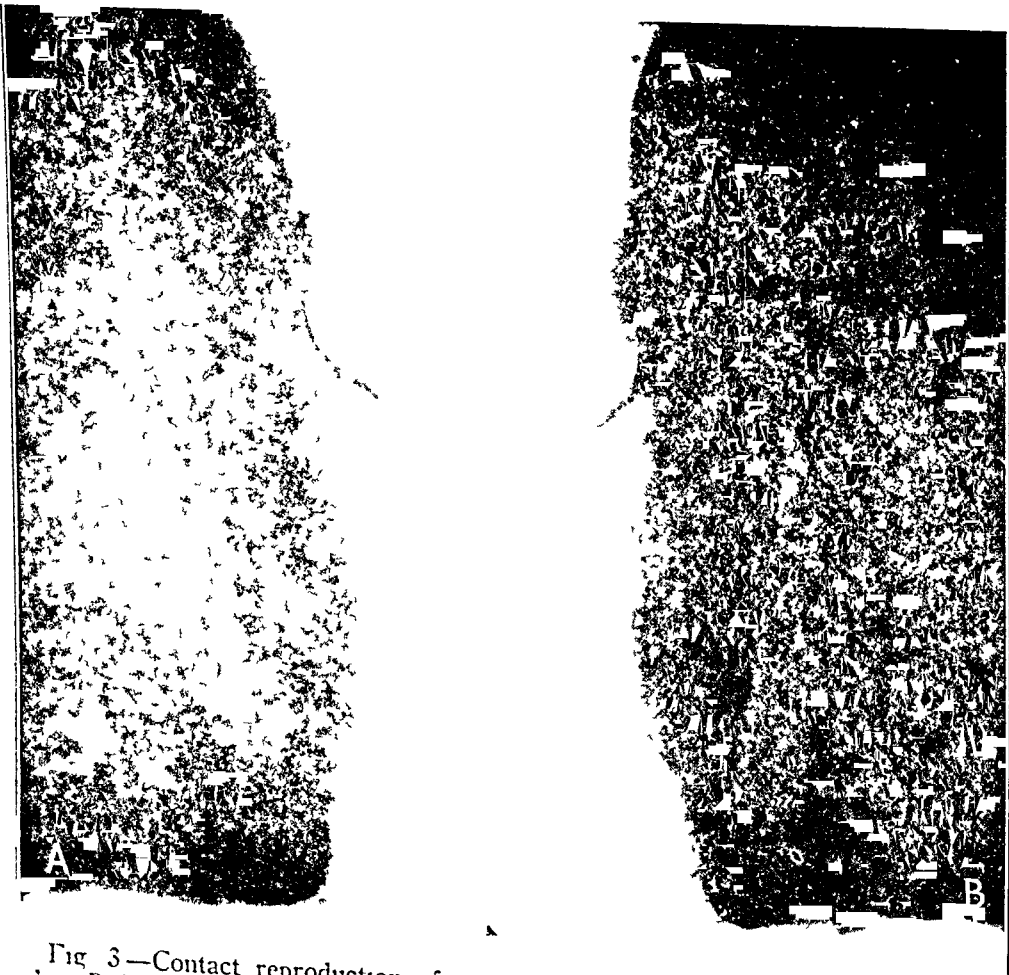


Fig 3—Contact reproduction of roentgenogram, soft parts technique A, right side B left side

complaint was no longer a simple statement like "I still get pimples on my face", rather it was an involved and sophisticated account of previous studies and treatments, both orthodox and self prescribed. This patient's approach to the physician was more like that of a physician himself to a competent technician or at least as one technically equal colleague to another. The patient made requests for recondite investigation (e.g., allergy tests on this occasion) and engaged in a cooperative weighing of new diagnostic and treatment possibilities. New diagnoses and treatments were grasped at eagerly. Needless to say, by this time all standard therapy, i.e., radiation (roentgen rays), vaccines, ultraviolet radiation, dietetic restrictions,



Fig 4.—Contact reproduction of roentgenogram of skin of cheek on dental film

traditional topical remedies and routines, had been received. It also goes without saying that the results have not been very satisfactory.

Dermatologic examination at the start of this course of observation and treatment showed a picture (fig 1) of some acne scarring, with very little frank acne activity, considerable traumatic scarring and neurotic excoriation (dermatitis factitia), rosacea-like erythema and telangiectasia. There were no milia. A diagnosis of *acne excoricee des jeunes filles* could apply. Cryotherapy and psychotherapy were suggested, planned and prescribed. The patient accepted gleefully.

It might have been easier, and I confess that the temptation was strong, to dismiss this patient as hopelessly maladjusted and therefore incurable, both derma-

tologically and psychologically. However, by evincing some sympathy I was soon rewarded by the presentation of something new in the form of several specimens of what looked exactly like grains of coarse sand (fig 2). The patient claimed that she extracted them from the skin of her face. At first I thought that here was a

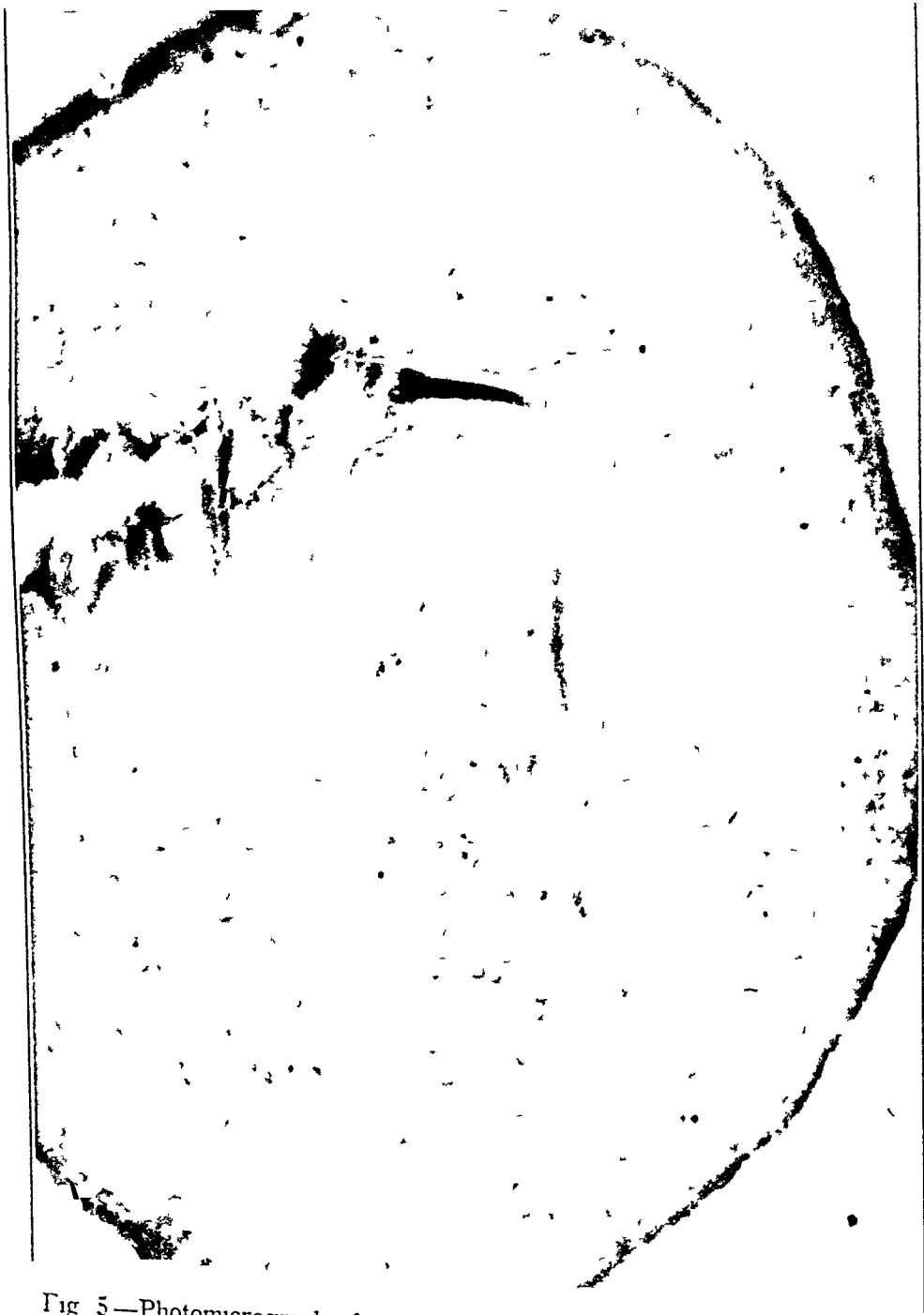


Fig 5—Photomicrograph of a sectioned osteoma (decalcified, stained by hematoxylin and eosin, \times about 125)

new dermatosis to report, namely, an unheard of case of "silicosis cutis." To the patient I suggested that she was palming off actual sand grains, perhaps even honestly and unconsciously deluding herself by a most skilful legerdemain. The patient was not to be shaken, however, and blandly recalled that she had extracted

such a pellet for the first time when she was 18 or 19 years old, but not again until very recently. Up to this writing about twelve separate grains or tiny pebble-like concretions have been submitted by the patient. She did not claim to be able to locate the deposits in her skin or to know exactly where or when one may be present or found. However, by hit or miss digging—and the word digging is literally descriptive of her assault on the skin, a sort of quarrying operation—she finds one or two from time to time. At no time could the patient point out a sure spot for biopsy or extract one of these bodies under direct observation. Biopsy of what was vaguely thought to be a likely spot in the patient's judgment showed no



Fig 6—Photomicrograph of a section of skin from the chin showing six osteomas in situ ($\times 202$)

bone on histologic processing. Examination of the skin under ordinary hand lens magnification and by palpation with most epicritical attention revealed no certain or reasonably likely places. However, roentgen examination of the skin of the face uncovered many tiny radiopaque (calcific) shadows in several places (figs 3 and 4).⁴

The specimens submitted by the patient were subjected to microchemical qualitative analysis and to microscopic examination after decalcification and section. The resulting observations proved that they were indeed spherules of typical bone (the table includes a pathologist's⁵ description and figure 5 shows the appearance

4 Dr William H. Meyer made the roentgenologic studies

5 Dr M. N. Richter made the pathologic examination

under the microscope) Finally, biopsy of the chin, with roentgenographic aid showed six osteomas in situ in about 1 cm (linear) of tissue (fig 6)

COMMENT

Until the bony deposits in this case were demonstrated in the skin of the face by soft parts roentgen technic, some critics of this case, putting great stress on the psychopathic habitus of the patient, were not convinced that the specimens she submitted were not marvelously contrived artefacts They even went so far as to call it "Bones (Bowen's) Disease" However, even without roentgenographic proof or proof by extraction under direct observation, it is inconceivable that anyone but an artisan of highest ingenuity could construct such pearl-like globules with the gross appearance and the orderly internal structure here seen to say nothing of the impossibility of inserting the microscopically demonstrable osteoblasts Despite the psychiatric vagaries of the subject involved and even without the conclusive objective observations, the case would be reasonably established

Until the cell structure of the specimens was resolved as that of typical bone, other critics expressed the belief that the concretions, even if genuinely plucked from the skin of the face, could be cutaneous calculi rather than osteomas Cutaneous calculi are said to occur in milia Ormsby and Montgomery's textbook⁶ contains a two sentence reference to such events as follows

In rare instances the deposition within milia of the salts of lime renders them as hard as cartilage (cutaneous calculi) These are usually of larger size [than ordinary milia, I suppose] and present a faint yellowish hue

Ormsby and Montgomery do not go on to state what the microscopic structure of such calculi might be, but I imagine, judging from salivary, ureteral and vesical calculi, that they must be rather structureless or crystalline if milia are merely retention products of sebaceous glands, or if not amorphous, then laminated like a geologic specimen or vaguely preservative of the epithelial onionlike capsular appearance of milia that are concentric or horny cysts In any event, this patient was devoid of milia clinically, and the microscopic picture of her concretions is indisputably more than these possibilities, i e., it is that of true bone Unless cutaneous calculi have been microscopically analyzed to be different from what has been herein conjectured above (and I know of no reference other than that in Ormsby and Montgomery), then Costello's case²⁵ suggests that bony hard concretions in milia are osteomas and not calculi It is possible, too, that Costello's case is not one of ossified milia despite the clinical resemblance, but rather multiple milia^{ary} osteomas of the face

⁶ Ormsby, O., and Montgomery, H. Diseases of the Skin, ed 6, Philadelphia, Lea & Febiger, 1943, p 1205

like Hopkins' case and much like mine—with the exception that in my case the concretions were not clinically detectable by surface examination

The pathogenesis of osteoma cutis is, of course, obscure. Speculation is all that can be offered but still may be worth while. First, it is well to recall that a distinction is made between metaplasia into bone and neoplasia of bone. Metaplastic ossification is fairly common and occurs readily enough secondary to calcification, chronic inflammatory processes and other preexisting irritative states. Neoplastic ossification is to be expected in malignant conditions of bone, but benign bony neoplasia (osteoma, osteosis) as it occurred in this case is undoubtedly rare. Theorization about embryonal rests of osteoplastic elements and nevus tardus development of such rests into true bone is inconclusive, but may be as near to the real situation as it is possible to come at the moment.

The only other suggestion that I can advance is that the condition in point is actually metaplasia after all, rather than neoplasia. The ossification may be conceived as being secondary to prolonged and persistent trauma in an area of skin that is exposed, that is well worked and hard working otherwise and that is rich in vascular structures and particularly rich in muscle elements. One may well imagine remembering the ossifying myositis of equestrians and the relative ease with which bone forms in bruised striated muscle generally, that continuous pressing, squeezing and scratching of the skin of the face by patients like the one of this report may result in chronic inflammation of some of the tiny muscles of striated or smooth variety that are plentifully present in the facial skin to give it expressiveness. In the course of time, some of these loci of damage may become calcified and eventually ossified into minuscule masses of bone, as here found.

RINGED HAIR

Report of a Case

ROYAL M MONTGOMERY, M D
NEW YORK

AND

ABRAHAM I BINDER, M D
LYNN, MASS

RINGED hair, or, as it is also termed, *pili annulati* and *leukotrichia annularis*, is an abnormality which has interested physicians for a hundred years, and its cause is still unsolved. Karsch,¹ in 1846, was the first to describe this anomaly and called it "ringel haare."

Galloway² in 1896 reported two brothers with this rare disease and was the first to state that it was hereditary. Since then, Cady and Trotter,³ Snell and Foley,⁴ Reyn⁵ and Juon⁶ reported ringed hair in several generations. Snell and Foley and Juon have traced its incidence through four generations. Cady and Trotter in 1922 wrote an extensive treatise on this anomaly.

Our case is the first to be reported in the American literature since Snell and Foley's paper in 1932 and the first recorded case in which the axillary hair was also involved. Scalp hair is the common site involved, though ringed hair has been noted in the beard. In rare instances, teeth and nail changes have accompanied ringed hair. Up to the present, including our patient and her sister, 87 cases of ringed hair have been reported. This includes cases without microscopic examination, reported by authors as occurring in families.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University

1 Karsch, A. F. F. *De capillitii humani coloribus quaedam, Gryphiae*, F. G. Kümcke, 1846, p. 39.

2 Galloway, J. Case Report of Ringed Hair, *Brit J Dermat* 8 437 (Nov) 1896.

3 Cady, L. D., and Trotter, M. A Study of Ringed Hair, *Arch Dermat & Syph* 6 301 (Sept) 1922.

4 Snell, G. D., and Foley, F. Inheritance of Ringed Hair, *J Hered* 23 155 (April) 1932.

5 Reyn, A. *Pili Annulati* Occurring as a Family Disorder, *Brit J Dermat & Syph* 46 168 (April) 1934.

6 von Juon, M. Eine Beobachtung familiären Auftretens von *Pili annulati*, *Dermatologica* 86 117 (Aug-Sept) 1942.

Ringed hair is not due to pigment deficiency or pigment atrophy, as there is an equal amount of pigment throughout the hair. Speiss,⁷ in 1859 first pointed out that ringed hair is due to the inclusion of gas bubbles in the medulla of the hair. The gas present in the medulla refracts the light making that area appear white. Subsequent reports all verify this observation but as yet no one has identified the true nature



Fig 1—Scalp showing alternate light and dark segments in the hair, especially in the area of the part

of the gas or how it is formed. However, Cady and Trotter stated the belief that it is most likely carbon dioxide because the segmented appearance disappears when the hair is immersed in 5 per cent sodium hydroxide.

REPORT OF A CASE

G. A., a woman aged 26 years, had the condition of the scalp observed by us since birth. She was first seen on March 7, 1946, at the New York Skin and Cancer Unit. The patient's only illnesses were chickenpox and mumps in childhood. The patient's tonsillectomy at 2 years resulted in the regrowth of the tonsils. She came to the clinic because of a blue-brown dirty discoloration of the distal portion

7 Speiss, A. cited by Landois, L. Des plotzliche Ergrauen der Haupthaare. *Virchows Arch f path Anat* 35: 575, 1866.

of the finger nails, which had been present for two years. A history was obtained revealing the use of a mercurial ointment on the nails. Discontinuance of the ointment resulted in normal nails.

A distinct dusty appearance of the patient's scalp hair was noticed. The hair appeared beaded. However, this appearance was caused by alternate light and dark segments in the hair. The condition was present throughout the scalp but was more prevalent in the posterior portion. The hair did not appear broken. The axillary hair appeared ringed macroscopically. The pubic hair was normal.

The father's scalp hair was normal. The sister's scalp showed typical ringed hair both macroscopically and microscopically. There was no history of similar appearing hair in any other member of the family.

Examination of the patient's scalp under filtered ultraviolet rays showed no unusual fluorescence. However, close inspection of a single hair under filtered ultraviolet rays revealed that the light areas fluoresced a dull white.

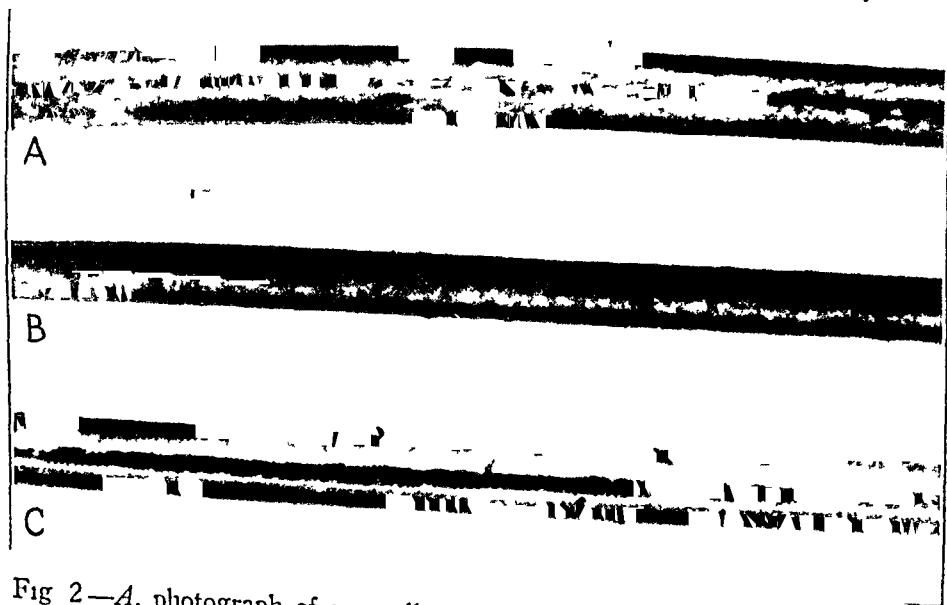


Fig 2—A, photograph of an axillary hair taken by transmitted light, showing typical dark segments in the medulla. Similar appearance in the hair of the scalp. B, photograph of normal brown hair taken by transmitted light. C, normal gray hair showing uninterrupted dark medulla, which was due to gas bubbles.

Microscopically, both the scalp hair and axillary hair presented uniform diameters, with no beading present. There was no atrophy or fragmentation of the hair. Throughout the entire length of both scalp and axillary hair were alternate light and dark areas in the medulla.

The light areas observed macroscopically (reflected light) were caused by the presence of gas bubbles in the medulla of the hair. Microscopic examination with reflected light revealed the gas bubbles to be present in the light areas. However, examination by transmitted light showed the areas in reverse, the former light areas appearing dark and the former dark areas appearing light.

SUMMARY

A case of ringed hair involving both scalp and axillary hair is reported. A sister also had ringed hair in the scalp.

57 W. Fifty-Seventh Street
52 Broad Street

FAVUS IN A RURAL COMMUNITY OF NEW YORK

SIDNEY J. ROBBINS, M.D.
NEW YORK

THREE cases of favus of the scalp were observed recently in Greenport, Long Island, 96 miles from the city of New York, with a population of approximately four thousand, five hundred. The community consists of a mixed population of both native and foreign born. The 3 cases of favus which were discovered there were all verified by mycologic examination. Cultures of the scales and hairs showed a growth of the causative organism, *Achorion schoenleini*, and on microscopic examination, the individual hairs from each patient yielded typical large spores in chains, with air bubbles attached. Favic chandeliers and chlamydospores were observed in the culture mounts in all 3 cases.¹

During the past twenty-five years there have been scattered reports of the sporadic incidence of the disease in many states.² However, favus has been seen much more frequently in Austria, England, France, Scotland, Russia and Poland. Bergeron³ stated that it is a disease of rural districts and that most patients with favus seen in large cities come from the country.

Aside from the comparative rarity of the disease, one of the interesting features of the minor epidemic which is here reported was the discovery of the carrier.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University (now New York University-Bellevue Medical Center).

1 Mrs. A. Casper, B.S., of the Skin and Cancer Unit, conducted the mycologic examination.

2 Dey, N. C. Notes on Common Skin Diseases. Ringworm of the Scalp, Favus, *Indian M. Gaz.* **76** 416-417 (July) 1941. Reque, P. G., Barefoot, S. W., and Conant, N. F. Tinea Favosa of the Scalp, *North Carolina M. J.* **2** 329-343 (July) 1941. Muskatblit, E. Tinea Favosa. Report of Six Cases, *M. Rec.* **151** 187-191 (March 20) 1940. Epstein, N. N., and Levin, E. A. Favus Infection. Report of a Case from California, *Urol. & Cutan. Rev.* **42** 515-517 (July) 1938. Lewis, G. M., Rosenfeld, H., and Hopper, M. E. Favus of the Glabrous Skin, *M. Rec.* **145** 189-191 (March 3) 1937. Kerr, P. S. Case Report. Favus in Native School Child, *New York State J. Med.* **35** 781 (Aug. 1) 1935. Tobias, N. Favus of the Scalp. Report of Cases, *J. Missouri M. A.* **26** 212-214 (May) 1929. Barrett, C. C. Incidence of Favus in Kentucky, *Arch. Dermat. & Syph.* **33** 126-127 (Jan.) 1936. Rutledge, W. W. Report of Case of Favus, *Kentucky M. J.* **34** 149-151 (April) 1936. Morris, G. E. Favus in Massachusetts, *New England J. Med.* **230** 667-669 (June 1) 1944.

3 Bergeron, cited by Ormsby, O. S., and Montgomery, H. *Diseases of the Skin*, Philadelphia, Lea & Febiger, 1943.

REPORT OF CASES

CASE 1—In June 1945, Miss D T, age 15 years, was seen by me in consultation with Dr J Mott Heath, Suffolk County Health Officer, and Dr William W Kaplan of Greenport, Long Island. She was a white girl, born in the United States, whose general health was good. She presented the typical clinical picture of favus with thick scales, scutula and areas of partial alopecia diffusely scattered over the scalp (fig 1). No significant abnormalities were revealed in general examination of the glabrous skin, appendages and nails. The duration of the disease was three years. A schoenleini was evident in microscopic examination of the hairs and in cultures. Examination of the scalp with filtered ultraviolet rays demonstrated a yellowish green dull fluorescence of scales and hairs. There were interspersed areas of atrophic alopecia. The patient was one of seven children. No other member of the family had favus.

The father of the patient volunteered the information that several other children in the village were known to have "ringworm of the scalp." He also stated that



Fig 1 (case 1) —A, before roentgen epilation, showing areas of atrophy, scaling, scutula and diseased hairs. B, view of scutula, diseased hairs and atrophic alopecia during defluvium after roentgen epilation.

his married daughter was now living in a house which had been previously occupied by a family whose members were known to have "ringworm." With this as a possible clue to the source of the favus infection, the county medical officer of the locality, Dr Heath, arranged to have all the members of the suspected family examined by me. The following 2 cases are of members of that family who were examined and proved to have the disease.

CASE 2—M N, a white boy aged 7, born in the same village, had, according to the mother, discolored hair since early infancy, although there had been no areas of baldness. Gross examination revealed patches of a greyish green discoloration scattered over the scalp (fig 2). There were no scales, although there was a mousy odor. There was no alopecia or atrophy. General examination of the glabrous skin disclosed no significant abnormalities. A yellowish green dull fluorescence was observed under filtered ultraviolet radiation. Favus was demonstrated in microscopic and cultural examination of the hair. Questioning of the

mother revealed that the father of the child had been suffering from a disease of the scalp since the age of 9. Thereupon an examination of the father was requested (case 3).

CASE 3—M. N., a white man aged 33, was the father of the aforementioned child (case 2). He was born in the United States, of Lithuanian parentage. Examination revealed a dollar-sized area of atrophy on the vertex of the scalp, with several hairs growing normally in the center. The remainder of the scalp was clinically normal. There was no fluorescence demonstrated with filtered ultraviolet radiation. Favus was demonstrated both microscopically and culturally on several hairs removed from the periphery of the atrophic area. The patient reluc-



Fig. 2 (case 2)—Discoloration of hairs without scaling or scutula

tantly admitted that the disease had been present since early childhood. About fifteen years previously he had consulted a local physician who had treated the area with roentgen rays, and the scales disappeared. A sister of the patient was examined and proved to be free of the disease.

COMMENT AND SUMMARY

Three cases of favus of the scalp are reported from a rural community with a population of four thousand five hundred, lying approximately 96 miles from the city of New York. All 3 patients were native born. The disease produced different clinical manifestations in each case, and microscopic observations were all similar. Although in the oldest

patient (case 3, the father) some local immunity to favus had evidently developed over a period of fifteen years and the disease had been localized to but one circumscribed area on the scalp, it was proved that he was the carrier, as evidenced by the presence of favus in his child (case 2) The fact that members of the two families shared the same house at different periods leads one to infer that the disease might have been transferred by an animal or parasite or that infected human hairs remained in the house

It has been suggested that further investigation be made of cats, rats, mice and other possible carriers in the community A more complete and careful examination of the local inhabitants has also been advised

30 East Sixtieth Street

ERYTHROPLASIA OF QUEYRAT

Report of Ten Cases

WILBERT SACHS, M D

AND

PERRY M SACHS, M D

NEW YORK

ERYTHROPLASIA is a rare disease and was first described in 1893 by Fournier and Darier¹ Since Queyrat's² studies in 1911, the disease has been known as erythroplasia of Queyrat Sulzberger and Satenstein,³ in 1933, reported the first case in the American literature Approximately 50 additional cases have since been presented at various dermatologic societies in this country, in addition to reports by Stiles⁴ and by Irgang and Alexander⁵

In spite of the rarity of cases, there has been considerable discussion concerning this disease It is our purpose in this paper to report our observations in 10 cases We intend to show that in these instances there was no clinical or microscopic evidence of malignancy or pre-malignancy and that lesions develop not only on mucous membranes but also on glabrous skin Suggestions as to therapy also are offered

The 10 patients reported here presented typical clinical pictures and previously had been given a diagnosis of and treatment for erythroplasia by many competent dermatologists The diagnosis was corroborated in 9 cases by microscopic examination However, in 1 case no biopsy was performed Several of the patients were presented before different dermatologic societies

We have omitted detailed descriptions of cases, as they prove repetitious and furnish little additional information to the following salient and pertinent features noted in our series All the patients were Jewish men, 25 to 50 years of age, who had lesions on the glans penis

From the Department of Medicine (Dermatology), New York Hospital and Cornell University Medical College

1 Fournier, A, and Darier, J Epitheliome benin syphiloide de la verge (epitheliome papillaire), Bull Soc franç de dermat et syph 4 324-328, 1893

2 Queyrat L Érythroplasie du gland, Bull Soc franç de dermat et syph 22 378-382, 1911

3 Sulzberger, M B, and Satenstein, D L Erythroplasia of Queyrat, Arch Dermat & Syph 28 793-806 (Dec) 1933

4 Stiles, F, Jr Erythroplasia of the Glans Penis (Queyrat), Arch Dermat & Syph 30 647-650 (Nov) 1934

5 Irgang, S, and Alexander, E R Erythroplasia of Queyrat in a Negro Report of a Case, Arch Dermat & Syph 34 247-250 (Aug) 1936

However, 3 patients also showed involvement of the scrotum (fig 1), 2 manifested patches on the shaft of the penis (fig 2) and 1 had a lesion on the lower part of the abdomen. Early lesions began as small erythematous macules or slightly elevated papules, about 0.5 cm in diameter. They extended peripherally, frequently covering the entire glans penis. The lesions appearing on the glabrous skin developed slowly and did not become large. Papules or patches of erythroplasia are red, shiny or velvety, not indurated and usually moist. There was no



Fig 1—Erythroplasia involving the scrotum

scaling, but often crusting. Subjective symptoms varied from complete absence of discomfort to severe stinging or itching. When the meatus was affected patients complained of burning on urination. The Wassermann and Kahn serologic reactions were negative. Two patients, in the history of their past illness, described generalized eruptions that indicated the possibility, in both instances, of exudative discoid and lichenoid chronic dermatosis. However, it is not our intention to imply any relation between the two diseases.

While in our series all were white men, the disease has been described in women and in Negroes. Erythroplasia has been reported in circum-



Fig 2—Erythroplasia of the shaft of the penis as well as the glans



Fig 3—Erythroplasia showing peg-shaped rete pegs, surface of the epidermis and the cellular infiltration ($\times 226$)

cised and in uncircumcised men. Additional sites for erythroplasia are the prepuce, oral mucosa, lips and vulva. Our microscopic studies were not limited to the cases reported here, but included several others of the same type, as well as 1 case of a lesion of the buccal mucosa and 1 of a lesion of the vulva. We have noted three histologic features that characterize erythroplasia: the shape of the rete pegs, the surface of the epidermis and the type of cellular reaction (fig 3). The epidermis



Fig 4—Erythroplasia showing the hydropic cells and the network-like appearance of the upper part of the epidermis ($\times 673$)

is irregularly and moderately acanthotic, with triangular or distinctly peg-shaped rete pegs. The surface consists of a loose network arrangement of the superficial epidermic cells. These cells are hydropic and swollen; the cytoplasm is clear, the nuclei lie free within the cell and appear normal and mitotic figures are not evident (fig 4). When the crust covers the surface the network-like architecture and the hydropic appearance of the cells are much less prominent. Inter cellular edema may be noted in the lower portion of the epidermis (fig 5).

The inflammatory reaction is in the upper and middle layers of the cutis, but it is most pronounced in the subepidermic region. The vessels are dilated, and a moderate interstitial edema is demonstrable. The cellular infiltration is perivascular, diffuse and usually moderately intense and consists predominantly of plasma cells. Small round cells and eosinophils may be present. Some of the cells may infiltrate into the epidermis.



Fig 5—Erythroplasia showing the crust formation on the surface of the epidermis ($\times 770$)

COMMENT

The patients with erythroplasia reveal no serologic, clinical or microscopic evidence of syphilis. Cellular infiltration composed mainly of plasma cells, which is seen in erythroplasia, may be present not only in syphilis but in many other dermatoses. Also, the vascular changes characteristic of syphilis are absent in erythroplasia. We believe that erythroplasia is not related to syphilis.

The dermatosis has been considered precancerous by almost all recognized dermatologic authorities. The French literature has fostered this view and has reported epitheliomatous development in practically all patients who could be followed for a sufficient number of years. A study of the cases recorded in this country revealed no definitely proved malignancy following erythroplasia. Moreover, 3 of our patients are cured, after the lesion had been present from three to five years. In 1 patient, the lesion persisted for fourteen years without any sign of carcinoma.

In our cases the microscopic picture showed no evidence of malignancy. Anaplasia, formation of whorls and pearls, keratinization, mitotic figures and dyskeratosis were absent. The hydropic state of the cells at the surface of the epidermis should not be construed as dyskeratosis. The reaction in the cutis is not that of an inflammatory protective zone, since it is diffuse and not limited to any particular region of the overlying epidermis. It is not different from any other inflammatory reaction, except that the cellular infiltration is composed chiefly of plasma cells.

Thus, the study of the few cases presented by us and those recorded in the American literature as yet lends no support to the concept that erythroplasia is an obligatory precancerosis or cancerosis. In fact, we are inclined to question this concept and believe that erythroplasia may be a productive inflammatory process and possibly a response to a specific agent.

TREATMENT

Perhaps this report is somewhat premature. We had hoped to outline a definite and distinct cure for the disease, but at present we cannot do so. Considering the presumed seriousness of this disease and since we have cured 3 and probably 4 patients, we have decided to submit the description of the therapy as far as we have progressed as a preliminary report. It should be stressed that occurrences of the disease are infrequent and that all except 1 of our patients previously had been treated for at least one and a half to fourteen years by competent dermatologists.

We entertained the thought that erythroplasia might be caused by an organism involving the vaginal tract, such as *Trichomonas* or a spirochete other than *Treponema pallidum*. We considered the possibility of a relationship to Vincent's infection. This concept was based on the location, behavior and some of the microscopic features of the disease. Since various factors prevented investigation we cannot attest to the validity of this concept.

Treatment with preparations with arsenic has been successful in *Trichomonas vaginalis*, Vincent's infection and spirochetal diseases. This led to the belief that the same therapy might be successful in erythroplasia. We have used neoarsphenamine intravenously, and neoarsphenamine tryparsamide, oxophenarsine hydrochloride and acetarsone.

(cinquarsen®) locally, all with beneficial results (Treatment with bismuth compound proved of little value) However, the best therapeutic effect was obtained with neoarsphenamine, 0.3 Gm dissolved in 4 cc of distilled water to which 1 cc of glycerin was added When arsenic compound was used in powder form or in glycerin alone the improvement was not pronounced

The aqueous solution of neoarsphenamine is swabbed on the lesion lightly twice a week for about two or three weeks Then it should be applied only when indicated by continued oozing The solution as described often may prove too strong and in these circumstances should be diluted three or four times It is important to remember that the arsenic compound should not be employed in too concentrated a form or for too long a period, because of excessive crusting that follows

After application of the solution the lesions become dry and form heavy crusts, which progressively develop into warty excrescences We have been unable to remove this crust without causing exacerbation In our attempts to separate the crust, we have tried boric acid wet dressings, boric acid ointment, solution of calcium hydroxide, isotonic solution of sodium chloride, cold cream, an oxycholesterol-petrolatum ointment base (aquaphor®), saliva, milk and other agents, but without success However, the crust disappears in time (up to two years), leaving no trace of the disease

The patients experienced no pain or discomfort The exudation and subjective symptoms disappeared within a few weeks and sometimes in a few days The solution seems to have no influence on the normal skin or the uninvolved portion of the glans penis We have seen no unfavorable reaction to this medication

A resume of the progress of the 10 patients shows that 3 are cured, 1 for over five years, another for three years and the last for one year We were unable to follow completely 2 patients, but we have reason to believe that 1 is practically if not entirely well Our first patient was treated in the conventional manner, because we were then unaware of the treatment herein suggested This patient has remained well for twelve years after superficial cautery of a lesion extending over most of the glans penis The remaining 4 patients are still under treatment Two are almost well, while the other 2 have been seen for only a short time

SUMMARY AND CONCLUSIONS

A new and nondestructive treatment for this disease with some apparent cures is outlined

Lesions of erythroplasia may develop not only on the glans but also on the shaft of the penis, the scrotum and the lower part of the abdomen We, like previous observers, believe that erythroplasia is unrelated to syphilis In contrast to other observers, we question the concept that erythroplasia is precancerous or cancerous

PARA-AMINOBENZOIC ACID AND INDOLE METABOLISM

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FOR THE past few years I have in private practice prescribed para-aminobenzoic acid in a variety of dermatoses, including hair and scalp conditions. A surprisingly common subjective response to this therapy has been a feeling of greater vigor, a loss of tired or enervated states. Some patients were so impressed with this result that they sought guidance in the use of the drug on other members of the family. My interest¹ in indole metabolism suggested a possible explanation of this subjective response on the basis of a reduction of protein putrefaction in the intestines with a consequent diminution in indole production.

Indole is a toxic substance, exclusively produced in the intestines by way of the bacterial degradation of the amino acid tryptophane. On absorption, approximately 50 per cent of it can be demonstrated as having been detoxicated by way of a conversion to the harmless indoxyl potassium sulfate (indican). The appreciable fraction of indole still unaccounted for after absorption represents the threat to the organism. Auto-intoxication is a word that has almost completely lost caste with clinicians (as has the adjective "bilious"), more because it lacks specificity in terms of cause as well as effect than because it is incompatible with concepts of pathogenesis.

Indole when ingested (5 mg) produces loginess, headache, malaise and fatigue. Indole intoxication must in my opinion be a clinical reality which clinicians disdain to search for in spite of the many indictments still pending against indole, including the one of carcinogenicity. With indican excretion in the urine as a gage of the indole production, the use of quantitative methods for the measurement of this elimination has clinically established several facts with respect to indole formation in the intestines. Chronic obstipation increases its production, as do diets high in animal proteins. Vegetable diets lead to low excretions of indican.

This research was made possible partly through a grant from The Doctor Simon Baruch Fund.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post-Graduate Medical School and Hospital (Dr Marion B. Sulzberger, Director).

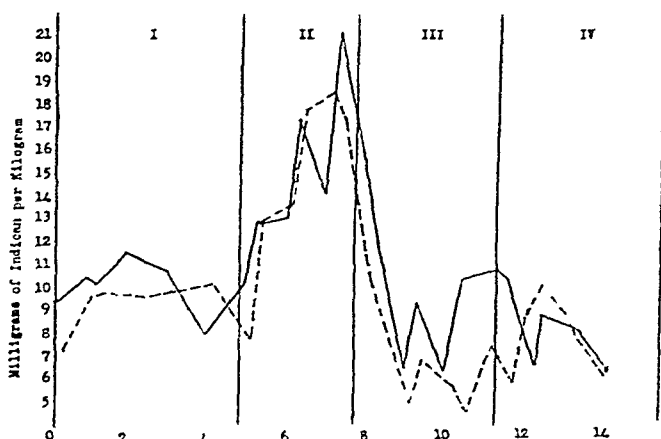
¹ Sharlit, H. A Method for the Quantitative Estimation of Indoxyl Compounds in Blood, *J Biol Chem* **104** 115 (Jan) 1934, The Concentration of Indoxyl Compounds (Indican) in Blood, *J Lab & Clin Med* **20** 850 (May) 1935, Indican Excretion in the New-Born, *Arch Pediat* **55** 277 (May) 1938.

Catharis causes a sharp fall in indican excretion for several days following its use

Para-aminobenzoic acid, accepted as a member of the vitamin B group, has been allegedly capable of affecting changes in the intestinal bacterial flora. The experiment conceived and herein reported sought evidence of a twofold nature (1) Can para-aminobenzoic acid influence the amount of indole production from a given standard diet, and (2) can para-aminobenzoic acid influence the degree of indole detoxication by its conversion to indican? While this conjugation of indole to indican involves hepatic function, no evidence exists demonstrating this functional capacity as exclusively hepatic

EXPERIMENT

Two groups (A and B) of rats were used. All urine was collected, in which samples the total quantity of indican² was determined. These amounts were recorded



Graph summarizing data in the experiment described. The unbroken line relates to group A (control rats) and the broken line relates to group B (rats fed para-aminobenzoic acid). The horizontal row of figures at the bottom represents time in weeks. In period I, a basic diet of ground fox chow was fed both groups. In period II, group A was fed an average of 1.80 mg of indole per rat plus the basic diet, group B received the same diet plus 15 mg of para-aminobenzoic acid per rat. In period III, both groups were given the basic diet. In period IV, group A was fed the basic diet and group B received fox chow plus 15 mg of para-aminobenzoic acid per rat.

as milligrams per kilogram of the average weight of the group. The time of the experiment was a continuous one, but divided into four parts.

For group A (control), part I was the control period to determine the amount of indican excreted on the standard diet, part II was the period in which indole was added to the standard diet, part III was the period in which the added indole had been removed from the diet and revealed the rate and time taken for the indican excretion to return to the base line, and part IV was a continuation of the study to

2 Sharlit, H. A Method for the Quantitative Estimation of Indoxyl Compounds in Urine. *J. Biol. Chem.* 99: 537 (Jan) 1933.

prove the stability of the base line reached in period III and to act further as control against period IV in group B

For group B (experimental), the same procedure was used as for group A except for the addition to the diet in periods II and IV of adequate amounts of para-aminobenzoic acid ("paba")

COMMENT

These facts, as well as the amount of indole and para-aminobenzoic acid exhibited, are revealed in the accompanying graph

The excretion curves for both groups were practically identical. One inference alone is permissible. Under the conditions of the experiment the exhibition of para-aminobenzoic acid influenced neither the production of the endogenous indole formed from the food protein nor the conversion of that or added indole to harmless indican by whatever organ (liver) or organs were involved.

This report is offered as representative of many pieces of work dealing with general medical problems being carried out in our dermatologic institution at the New York Post-Graduate Medical School and Hospital. It has been and continues to be our principle that dermatologists are both equipped and obligated to study general medical problems related to their field, and the problems of the metabolism of para-aminobenzoic acid, a substance used by skin specialists as a sun screen, as an anti-gray-hair factor and in other ways, properly comes within that category. In consonance with the principle just mentioned, Dr. MacKee has these many years made funds available to me for investigations dealing with fundamental metabolic and biochemical studies.

HEMANGIOPERICYTOMA

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STOUT and Murray,¹ in 1942, described a type of vascular tumor characterized by the formation of endothelial tubes and sprouts surrounded by closely packed, rounded and at times elongated cells. They demonstrated by tissue culture that these cells are derived from the capillary pericytes of Zimmerman² and suggested hemangiopericytoma as a properly descriptive name.

Various types of cells are closely applied to the outer surfaces of the capillaries, which in turn are composed of a single layer of endothelial cells. The pericapillary cells consist of connective tissue fibroblasts, histiocytes, mast cells, plasma cells, undifferentiated mesenchymal cells and in some instances an additional type of cell which has been called the Rouget cell and which, more recently, has been designated the pericyte. This contractile cell is spider-like, having numerous slender processes of a dendritic nature which encircle the capillary and serve to change the caliber of the lumen² (fig 1). Using a silver chrome impregnation Zimmerman showed similar cells, which he called pericytes, encircling the capillaries of the human heart. He wrote that these cells were contractile and that they were modified smooth muscle cells. In man, pericytes have been demonstrated in the kidney, liver, heart, lung, intestine, pia mater and omentum³.

The adventitial cells of blood vessels are not pericytes, but are fixed stellate connective tissue cells.

Dr Stout and Dr Murray assisted in this work.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1 Stout, A P, and Murray, M R. Hemangiopericytoma, *Ann Surg* **116** 26 (July) 1942.

2 Zimmermann, K W. Der feinere Bau der Blutcapillaren, *Ztschr f Anat u Entwicklsgesch* **68** 29, 1923.

3 (a) Zimmermann² (b) Stout, A P, and Cassel, C. Hemangiopericytoma of the Omentum, *Surgery* **13** 578 (April) 1943.

Murray and Stout⁴ have shown by tissue culture that the epithelioid cells of the glomus tumor are derived from Zimmermann's pericyte, and this led them to the investigation of other vascular tumors with cells arranged peripherally about the vessel walls. They¹ have reported 8 cases of hemangiopericytoma of the skin, 1 of the deep tissues of the thigh and 1 case of hemangiopericytoma of the omentum^{3b}

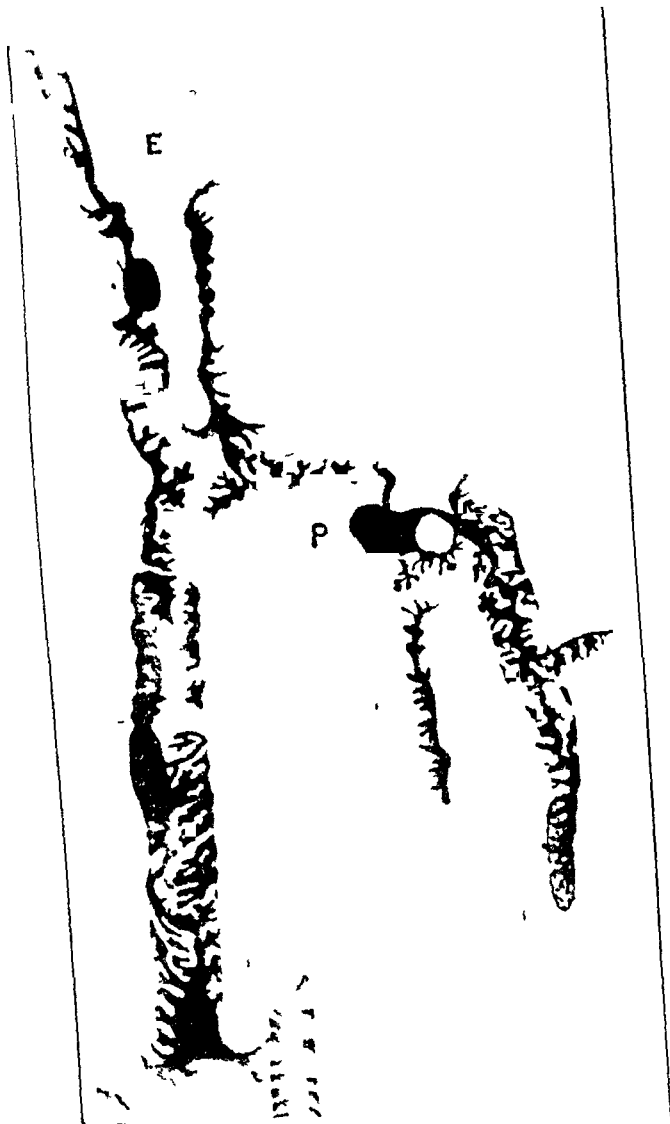


Fig 1 (redrawn from Zimmermann)—Capillary and precapillary pericytes in the heart of a 43 year old man *E*, endothelial cell, *P*, pericyte

Four of these tumors were composed of endothelial tubes and sprouts, surrounded by pericytes. All four were excised without known recurrence. These tumors had, in addition to the rounded pericytes, certain areas in which the cells were spindle shaped and resembled smooth

4 Murray, M. R., and Stout, A. P. The Glomus Tumor. Investigation of Its Distribution and Behavior, and the Identity of Its "Epithelioid" Cell, *Am J Path* 18 183 (March) 1942

muscle cells In some of them blood vessel tumors there was a probable relationship between pericytes and smooth muscle cells, because the cells arranged about the tumor vessels ranged from the usual round pericyte through an intermediate form of spindle-shaped cells to a fully differentiated cell with myofibrils In their¹ cases 5, 6 and 7 the observations in the histologic examination suggested strongly that the pericyte is related to the smooth muscle cell The next step in differentiation would be represented by a tumor with no round pericytes, but composed mainly of fully differentiated smooth muscle cells Tumors of this sort do exist and have been studied and discussed by Stout as cutaneous leiomyomas⁵ At that time the close relationship between those leiomyomas and their more recent group of hemangiopericytomas was not appreciated

Stout and Murray stated in their report on hemangiopericytoma¹ that some of the tumors were excised without known recurrence Their eighth case exhibited infiltrative growth Ten operations had been performed within eleven years in attempting to remove a small tumor on an index finger, and the eleventh operation consisted of amputation of the finger with removal of three fourths of the metacarpal bone Pericytes were the most conspicuous feature of the tumor and were arranged in lobules surrounding the vessels and endothelial sprouts Their ninth patient had a tumor of the thigh which had been present three years and which measured 14 by 7 by 6 cm when excised There was no local recurrence, but four years later there were observed in the liver five nodules, on one of which a biopsy was performed The liver was treated with small doses of roentgen rays The patient, whose health grew progressively poorer, died seven years after the first operation The primary tumor and the metastatic node from the liver were composed of many endothelial tubes surrounded by closely packed rounded cells

Pericytes are one type of cell in the perithelium there are several others, and the perithelial origin of other types of tumors has been investigated Becker and Thatcher⁶ in 1938, showed by tissue culture that Kaposi's sarcoma is a multicentric neoplasm apparently originating from embryonic mesenchymal cells (lymphoid cells of Marchand) These cells arise in the perithelial tissue and are but one of several types of cells making up the perithelium In the development of the human embryo not all mesenchymal cells form mature cells, some remain undifferentiated and arrange themselves along blood vessels In tissue culture and in inflammation they undergo progressive develop-

5 Stout, A P Solitary Cutaneous and Subcutaneous Leiomyoma, *Am J Cancer* **29** 435 (March) 1937

6 Becker, S W, and Thatcher, H W Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, *J Invest Dermat* **1** 379 (Oct) 1938

ment and furnish new cell types. These cells probably include the so-called pericyte (contractile cell of Rouget) and the undifferentiated cells of Marchand and those of Maximow.⁷ Many different types of tissue cells are arranged along the capillaries: fibroblasts, histiocytes, undifferentiated mesenchymal cells, mast cells, plasma cells and pericytes. All these are considered as perithelium.

The hemangiopericytoma is a vascular tumor without sufficiently characteristic gross features to enable it to be recognized clinically, and

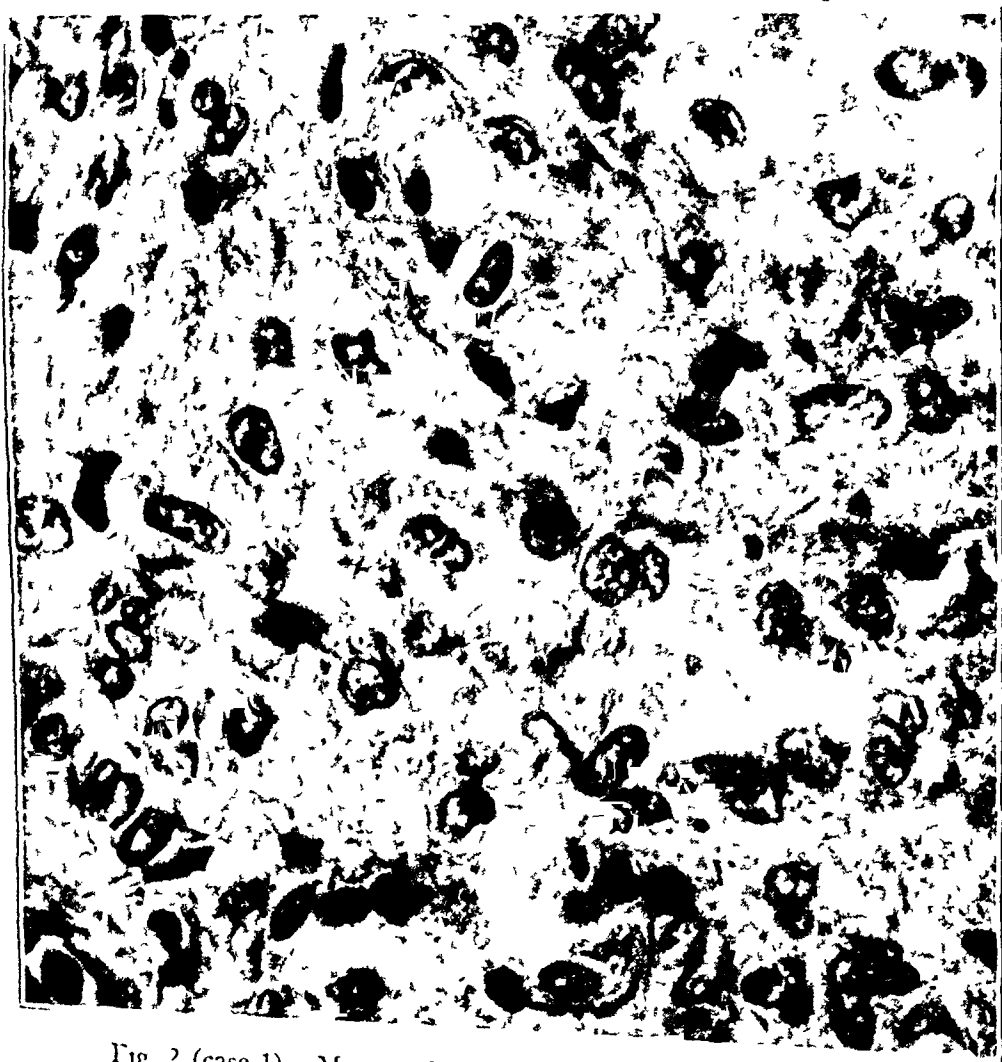


Fig 2 (case 1)—Masses of pericytes surrounding vessels $\times 775$

the diagnosis must be made by histologic examination. Clinically it may resemble granuloma pyogenicum, hemangioma, lymphangioma, angiosarcoma, glomus tumor or hemangioendothelioma.

REPORT OF CASES

CASE 1—(Dr A. P. Stout has permitted reporting of this case) A tumor of the mons veneris had been growing in the subcutaneous tissue of a 43 year old

⁷ Maximow, A. A. and Bloom, W. A Textbook of Histology, ed 3, Philadelphia W. B. Saunders Company, 1938, p 232, fig 201

woman for at least seven years. When excised, it was kidney shaped and measured 7 by 5 by 3 cm, and the tissue surrounding it was exceedingly vascular. It was a soft solid pinkish growth, mottled with red. There has been no recurrence in two years.

Figures 2 and 3 show that throughout the corium there were numerous dilated blood vessels of varying caliber. These vessels were surrounded by an enveloping mantle of cells, some of these were round or oval and others appeared spindle shaped. At some points these cells were closely packed and at others less so. Their nuclei for the most part corresponded to the shape of the cell. They contained one

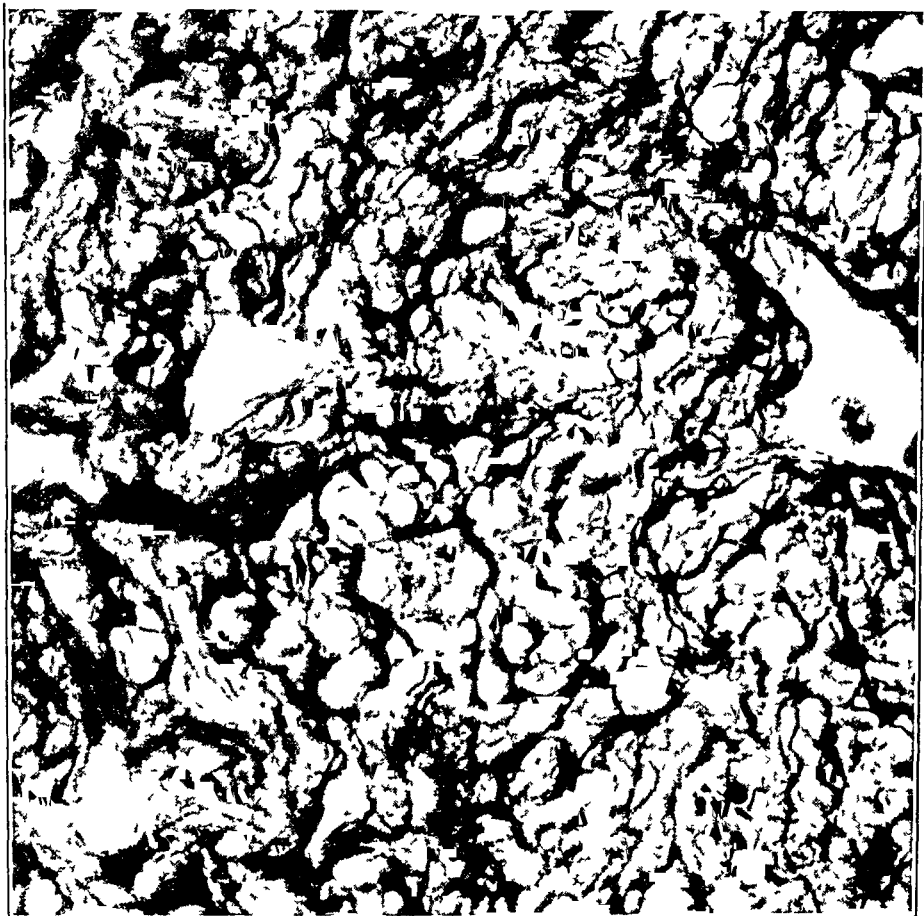


Fig 3 (case 1).—Reticulum (Laidlaw) stain showing reticulum fibers surrounded by pericytes $\times 775$

or more nucleoli and a chromatin network which stained fairly well. The Laidlaw reticulum stain showed that the enveloping cells were outside the reticulum fibers.

CASE 2—This case is interesting because it seems to represent a composite tumor of both pericytes and endothelial cells.

A 12 year old white boy was first seen in the New York Skin and Cancer Unit on Jan 13, 1945. He complained of a painless growth of six months' duration, located over the left scapula. There had been frequent bleeding, both spontaneous and after slight trauma. The lesion consisted of a solitary firm reddish purple sessile sharply circumscribed nodule. It was 1 cm in diameter and raised 0.7 cm

above the surrounding skin. The top was covered with a black crust. A diagnosis of granuloma pyogenicum was made, and the mass was destroyed by electrodesiccation. The patient returned to the clinic ten months later, on October 12. There were multiple recurrences which had been present four months, confined to the area in the vicinity of the original growth. Again, there had been frequent spontaneous bleeding. In a fan-shaped area (fig 4) approximately 4 cm in diameter

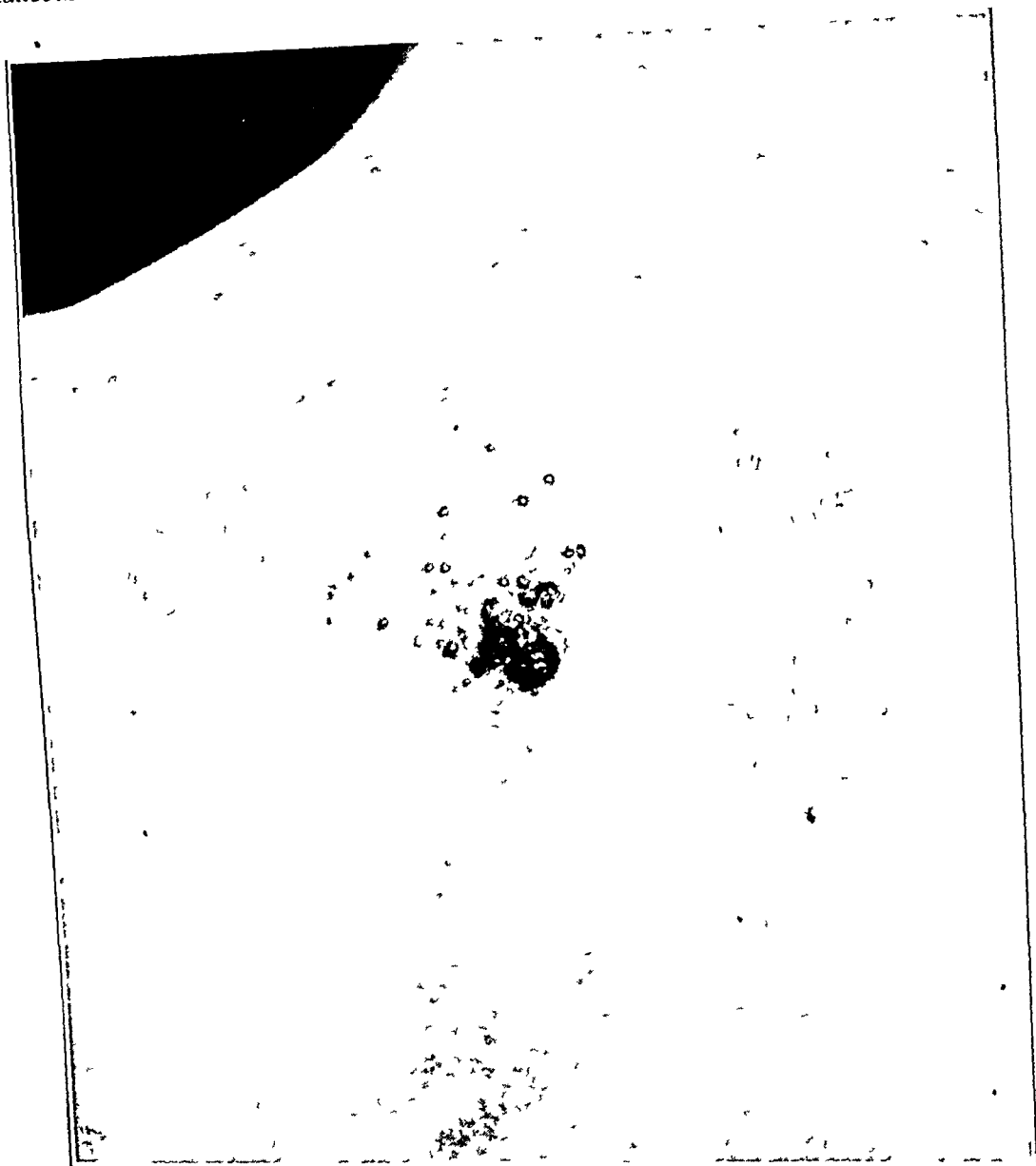


Fig 4 (case 2)—Multiple recurrences in area of original growth. Follicular lesions of irritation from adhesive tape are apparent.

were many discrete sharply circumscribed papular lesions, with intervening normal skin. The two largest nodules were at the apex of the fan-shaped area and were contiguous, hemispheric and bright red. They had a cauliflower-like surface covered with a fibrinous purulent exudate. Extending upward and outward toward the left shoulder were thirty to thirty-five fresh lesions, their size varying from that of a pinhead to that of a match head. These were dome shaped, bright red and raised 1 to 2 mm above the surrounding skin. The satellites became smaller as they extended outward from the original site. Just superior to the largest

nodule there was a bluish scar at the site of the desiccation of the original tumor. Three areas of irritation from adhesive tape were noted, showing follicular papulopustular lesions. A biopsy was performed.

Histologic examination showed, in the upper and middle layers of the corium and in the upper third of the deepest layer, several well defined but irregular masses (fig 5). One of these was composed of numerous capillaries. These were lined with a single layer of endothelial cells with round nuclei which projected into the lumens of the vessels, some of which were filled with red blood cells. The intervascular stroma was in part normal and in part rather loose and spongy. Scattered throughout the stroma there was a sparse cellular reaction composed of small, round and occasional wandering connective tissue cells. The epidermis above this tumor tissue was rather thin, with obliterated rete pegs and papillary bodies.



Fig 5 (case 2) —Photomicrograph of one of the tumor lesions \times approximately 260

In another part of the section there were several other well defined irregular tumor deposits which, with the low power of the microscope, appeared denser and contained fewer capillaries than in the aforementioned areas. These capillaries were surrounded by a dense mass of cells which appeared to envelop the vessel. With higher magnification (fig 6) these cells appeared, for the most part, rounded or oval, with a similarly shaped nucleus and a small amount of cytoplasm. Some of the cells were spindle shaped, with a corresponding oblong nucleus. The nuclei of these enveloping cells contained a moderate amount of chromatin and one or several nucleoli. No mitotic figures were visible. Few of the usual inflammatory cells were present. The epidermis above these areas appeared unchanged, and the surrounding collagenous framework revealed no noteworthy changes. With

the Wilder reticulum stain, numerous fine and coarse dark-staining reticulum fibers could be observed. At some points the cells appeared outside and at others inside the reticulum fibers (fig 7).

On November 8, a piece of tissue was removed for tissue culture and submitted to Dr Stout and Dr Murray, together with slides from the biopsy. They concluded that the tumor was of a composite type, composed of pericytes and endothelial cells.

The lesions were treated with three separate exposures of roentgen rays filtered through 2 mm of aluminum, approximately 425 r being given at each treatment, one month apart. There was complete involution of all vascular lesions, except for some small grouped skin-colored remnant tags. An area of hyperpigmentation about 2 inches (about 5 cm) square was also noted (fig 8).

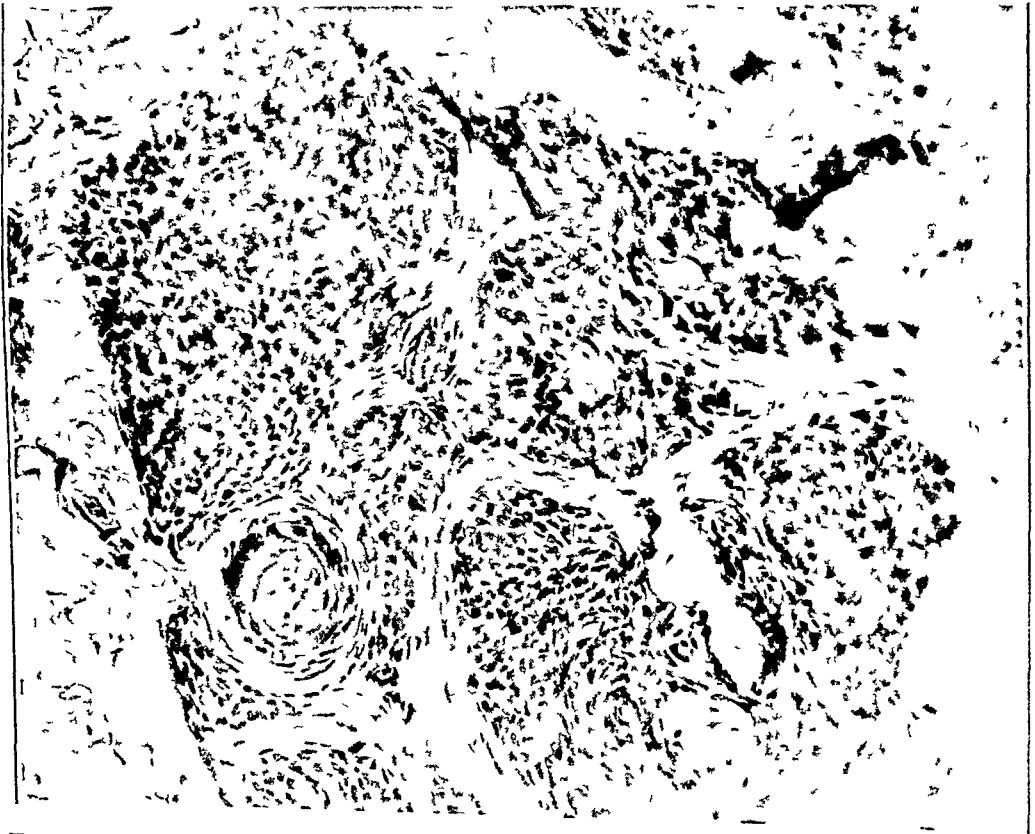


Fig 6 (case 2)—Photomicrograph of the lesion in figure 5. \times approximately 186.

DIFFERENTIAL DIAGNOSIS

Since it is almost impossible to make a diagnosis of hemangiopericytoma clinically and since the diagnosis can be made positively only by microscopic examination, the lesions which it resembles and for which it might be mistaken are described in the following paragraphs.

Granuloma Pyogenicum Granuloma pyogenicum usually begins at a point of trauma. It appears as a raised, red to wine-colored, usually pedunculated solitary lesion, with a slightly irregular surface. After removal it may recur, but usually at the original site and never with satellite lesions as in hemangiopericytoma. Histologically granuloma pyogenicum is composed of numerous dilated capillaries of varying

sizes which are separated by a rather loose intervascular stroma, within the meshes of which polymorphonuclear leukocytes, small round cells and wandering connective tissue cells may be observed. The vessels are composed of a single layer of endothelial cells which, at times, may be edematous. No mantles of pericytes are present surrounding the vessels as in hemangiopericytoma.

Angioma. Angioma usually begins in early life. Its appearance varies from a raised soft raspberry-like lesion to the somewhat bluish deep-seated cavernous type. The lesions vary in size from a pinhead



Fig 7 (case 2) —Wilder reticulum stain of the lesion in figure 5. \times approximately 189.

to a walnut or larger. They may be single or multiple. Differentiation can be established on histologic grounds only. Histologically angioma is composed of blood capillaries, the walls of which consist of a single layer of endothelial cells. The supporting connective tissue stroma is fairly close to normal. The capillaries do not have a mantle of pericytes as in hemangiopericytoma.

Lymphangioma. Lymphangioma is composed of soft opalescent vesicle-like grouped compressible lesions which vary in size from a pinhead to a millet seed and from which lymph may be aspirated. Histologically lymphangioma is composed of lymph capillaries of vary-



Fig 8 (case 2) —Involution of satellites and original lesion after filtered roentgen therapy, showing squared area of hyperpigmentation

ing size The supporting stroma is fairly close to normal } No mantle
of pericytes is demonstrable as in hemangiopericytoma

Angiosarcoma—Angiosarcomas may be single or multiple and appear on any part of the body They are relatively soft and vary in size from a pea to a walnut and at times are larger Their color may vary from a pale pink to a deep wine red They are slow growing and not common Histologically angiosarcoma is a tumor which presumably arises from the perithelial cells of Eberth in the adventitial lymph spaces It does not arise from the pericytes of Zimmermann The neoplastic mantle around the cells can be demonstrated to be composed of the former rather than the latter

Glomus Tumor—Glomus tumor is usually a solitary bluish somewhat firm lesion which varies in size from a pinhead to a small pea It occurs most commonly on the extremities and is associated with considerable pain and tenderness It does not commonly recur after excision Histologically glomus tumor is composed of a more or less typical structure similar to the normal glomus The most prominent change is the proliferation of the so-called epithelioid cells According to Stout and his co-workers the epithelioid cells are pericytes While hemangiopericytoma presents a hyperplasia of pericytes it does not have the structure of a glomus

Hemangioendothelioma—Hemangioendotheliomas may cause some difficulty in differentiation from a hemangiopericytoma, particularly from a clinical standpoint They may be solitary or multiple and may vary in size from a pea to a lemon They are fairly soft, are usually burgundy red in color, bleed easily, may ulcerate and may be surrounded by satellites They may occur on any part of the body and are most frequently observed in children Histologically hemangioendothelioma is a tumor composed of neoplastic endothelium Neoplastic endothelium may proliferate within the lumen of the vessel, may invade the vessel wall or may proliferate outside the wall However, endothelial cells, of which the tumor is composed, retain their histologic appearance, and they do not have the characteristics of pericytes In hemangiopericytoma the endothelium is composed of normal endothelial cells which never invade the vessel wall

SUMMARY AND CONCLUSIONS

The hemangiopericytoma is a vascular tumor characterized by the formation of endothelial tubes and sprouts, with a surrounding sheath of rounded and sometimes elongated cells They are derived from the capillary pericytes described by Zimmermann The pericyte of Zimmermann has been shown to be the origin of the enveloping mantle of cells in the glomus tumor, the hemangiopericytoma and the cutaneous and subcutaneous leiomyomas Diagnosis is difficult to establish on

clinical grounds, but on histologic grounds the diagnosis can be made with the aid of hematoxylin and eosin stain, Wilder reticulum stain or Laidlaw stain and tissue culture. It is possible to have a blood vessel tumor composed both of pericytes and endothelial cells.

In our case of a composite tumor roentgen irradiation appeared to be of definite value, but it is too early to comment on the permanency of the result. For this reason and because of the danger of recurrence and especially metastasis, wide scalpel excision is the probable therapeutic method of choice.

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EXTRACELLULAR CHOLESTEROSIS WITH PULMONARY INVOLVEMENT

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AND

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EXTRACELLULAR cholesterosis is a rare chronic systemic disturbance of lipid metabolism in which, for some as yet unknown reason, cholesterol finds its way into the tissues causing a definite clinical and histopathologic picture

Urbach¹ investigated and reported the first case of this disease and also named it. This case had previously been described by Kerl² and subsequently was again reported by him³. Search of the literature does not show any other report until that made by Laymon⁴. Two cases in which the condition resembled this disease were reported by Levin,⁵ and Frost and Anderson,⁶ but the diagnoses were never fully confirmed. Rosen⁷ had a patient under observation for many years who presented the chief features of this condition. It is our impression that there have been other examples of this disease which were unrecognized.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital (Dr Marion B Sulzberger, Director)

1 (a) Urbach, E, Epstein, E, and Lorenz, K. Beitrage zu einer physiologischen und pathologischen Chemie der Haut. Extrazellulare Cholesterinose, *Arch f Dermat u Syph* **166** 243-272, 1932. (b) Urbach, E. Lipidstoffwechselerkrankungen der Haut, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1932, vol 12, pt 2, pp 320-330, (c) Kutane Lipoidosen, *Dermat Ztschr* **66** 371-386, 1933.

2 Kerl, W. Multiple Knotenbildung, Reichlich Lipoidenthaltend, *Zentralbl f Haut- u Geschlechtskr* **36** 37, 1931.

3 Kerl, W. Ueber eine neuartige generalisierte Lipoid-Infiltration mit Vorwiegender, zum teil Knotenformiger Beteiligung der Haut und Schleimhaut, in Neisser, A, and Jacobi, E. *Ikonographia Dermatologica*, Berlin, Urban & Schwarzenberg, 1932.

4 Laymon, C W. Extracellular Cholesterosis, *Arch Dermat & Syph* **35** 269-284 (Feb) 1937.

5 Levin, O L. A Case for Diagnosis (Extracellular Cholesterosis?), *Arch Dermat & Syph* **44** 733 (Oct) 1941.

6 Frost, K, and Anderson, C R. Extracellular Cholesterosis of Urbach, *Arch Dermat & Syph* **39** 1061 (June) 1939.

7 Rosen, I. Personal communication to the author.

REPORT OF A CASE

A C, a white married woman, aged 23, born in the United States, was first seen at the New York Skin and Cancer Unit Jan 16, 1948. The patient presented an eruption which began in March 1947, at which time she was pregnant five months. The eruption first appeared on the knees in the form of several painful "red bumps." In June similar changes developed on the buttocks, and by October new lesions appeared gradually in the following sequence: legs, over the interphalangeal joints



Fig 1—Extensive brownish blue discoloration, with thickening and slight scaling of the skin. Nodules show superficial necrosis.

of the fingers and toes, elbows, thighs and left side of the neck. At this time, after an intratracheal study with iodized poppyseed oil, all the affected sites increased in size, severity and tenderness, and many ulcerated within a short time. With the exception of the affected areas on the thighs, buttocks and neck, there was no tendency toward spontaneous healing.

There was no history of serious illness until the age of 13. After a tonsillectomy, a productive cough developed, which had been present almost continuously. The

patient's only pregnancy, previously mentioned, terminated normally in a healthy child. The familial history on both sides did not reveal a similar cutaneous condition or metabolic disorder.

The patient was first treated for the cutaneous complaint by her family physician who gave a diagnosis of erythema multiforme. There was no improvement with topical treatments, internal therapy or 1 skin erythema unit of roentgen rays given over a period of four weeks. On Oct 8, 1947, she was hospitalized for two weeks at Newark, N J, because of the exacerbation of the cutaneous disease and loss of weight, fever and severe cough. From a biopsy specimen taken at that time from a lesion on the buttock the diagnosis was erythema multiforme with secondary pustule.



Fig 2—Nodules on knuckles

lation. The roentgenologic observations, including those in studies with iodized poppyseed oil, suggested the possibility of pulmonary tuberculosis, although on clinical grounds other diagnoses were considered. Roentgenograms of the hands showed them to be normal. Repeated examinations of the sputum and gastric washings failed to show tubercle bacilli. At the hospital she received 20 Gm of streptomycin in divided doses, which improved the pulmonic symptoms, but not the cutaneous disease.

On the patient's admission to the New York Skin and Cancer Unit the cutaneous observations were limited to the dorsa of the fingers and toes, elbows, knees, legs, ankles, back of the thighs, buttocks and left side of the neck. The mucosae were not affected. On the left side of the neck, thighs and buttocks the lesions had healed with coin-sized, irregularly shaped, superficial pigmented scars. Both legs

showed extensive brownish blue discoloration, with thickening and slight scaling of the skin (fig 1) Lesions about one to two weeks old on the ankles consisted of elevated firm brownish blue papules and nodules, split pea to quarter size, exquisitely painful on pressure Well advanced nodular lesions present on the legs were foul-smelling and necrotic, some showed deep ulcerations and others a black crust On the knuckles (fig 2) and toes there were present dime-sized to nickel-sized sharply circumscribed moderately elevated firm reddish yellow nodes, the surfaces of these were uneven and scaly and had undergone superficial necrosis On the elbows and knees there was noted a plaque-like formation, consisting of coalesced papules and nodules, some assuming annular shapes

On physical examination the patient appeared somewhat pale, underweight and frail Except for the described lesions positive observations were confined to the chest dullness over both upper lobes with diminished breath sounds and many coarse moist rales, a few were also present at both bases The liver and spleen were not palpable, and there was no adenopathy Eye ground observations were normal

Laboratory Observations—The blood cell count on Jan 28, 1948, showed red blood cells 5,830,000, hemoglobin 12.5 Gm per hundred cubic centimeters, white blood cells 17,750, with 75 per cent polymorphonuclear neutrophils, 1 per cent polymorphonuclear eosinophils, 17 per cent lymphocytes and 7 per cent monocytes Pronounced achromia, anisocytosis and poikilocytosis were noted The differential count on February 24 showed 18,000 leukocytes, 71 per cent polymorphonuclear neutrophils, 1 per cent polymorphonuclear eosinophils, 12 per cent lymphocytes, 5 per cent monocytes and 11 per cent band forms The sedimentation rate was 25 mm per hour (normal 15 mm per hour) The basal metabolic rate on February 1 was -12 per cent Two separate blood serologic tests for syphilis elicited negative reactions Urinalysis showed no abnormalities, with polariscopic examination no double-refractile bodies were found On Jan 23, studies of the chemical content of the blood were total lipids, 337 mg (normal 500 to 700), fatty acids, 249 mg, cholesterol, 90 mg (normal 160 to 230), of which 35 per cent consisted of cholesterol esters, nonprotein nitrogen, 24 mg, urea, 8.5 mg, creatinin, 1 mg, and sugar 70 mg per hundred cubic centimeters On February 6, total cholesterol was 120 mg per hundred cubic centimeters, of which 50 per cent were cholesterol esters On February 6, tests of hepatic function showed cephalin flocculation 1 plus (doubtful), thymol turbidity 3 units (normal) and galactose tolerance normal

Reactions to intradermal tests with old tuberculin in 0.1 cc doses, ranging from 1:1,000,000 to 1:100 dilutions, were negative The reactions to intradermal tests to coccidioidin and histoplasmin antigens were negative Smears, cultures and guinea pig inoculations of the sputum failed to show tubercle bacilli Direct mount and culture revealed no pathogenic fungi Chemical examination of the sputum showed 571 mg of cholesterol per hundred cubic centimeters, double refractile bodies were present on polariscopy

Roentgen examination of the chest (fig 3) showed both lung fields to contain predominantly productive infiltrations which were partly confluent in the first right intercostal space Several small nodular shadows were seen in both upper lung fields, the largest one underlying the fourth left anterior rib, measuring 1 cm in diameter Roentgen examination of all bones of the upper and lower extremities revealed them to be essentially normal

Chemical examinations for cholesterol in the excised skin were made by the Sperry-Schonheimer acetone-alcohol method On February 26, a large piece of affected skin was removed from the right knee, trimmed of subcutaneous fat and analyzed The laboratory reported total cholesterol, 151 mg (wet tissue), free

cholesterol 128 mg and cholesterol esters 0.23 mg per hundred cubic centimeters. Polariscopic examination showed no double refractile bodies. On February 29, a piece of apparently normal skin from a nonaffected area on the chest of the patient was excised and reported as containing total cholesterol, 0.76 mg, free cholesterol, 0.60 mg, and cholesterol esters, 0.16 mg per hundred cubic centimeters. On March 18, a piece of skin from a normal person was removed and showed total cholesterol, 0.67 mg, free cholesterol, 0.42 mg, and cholesterol esters, 0.25 mg per hundred cubic centimeters.

Histologic Studies—A well advanced nodule removed from the right knee was examined by Dr. Charles F. Sims, who reported as follows: The hematoxylin and eosin stain revealed that almost the entire cutis was the seat of a massive cellular infiltrate (fig. 4). This process was more intense toward the epidermis, shading



Fig. 3—Roentgenogram showing infiltration of both lung fields

off into the deep cutis. The connective tissue framework was almost indiscernible and appeared homogenized with intense red, particularly in the upper part of the corium. The elastic tissue (Weigert's stain) was practically nonexistent in the heavily infiltrated areas. The cellular infiltrate was made up mainly of enormous numbers of polymorphonuclear leukocytes, together with lymphocytes, round cells, wandering connective tissue cells and fibroblasts. No giant or foam cells were noted. There was fragmentation of nuclei. The tissue spaces were packed with these cells, especially around the coil glands. Scattered throughout the reaction were many dilated and congested blood vessels with swollen endothelium. The density of the infiltrate obscured the perivascular reaction, in places, the vessels were surrounded by lakes of edema and fibrin. The epidermic changes were not distinctive, merely showing flattening and slight disorganization in the cells of the basal layer. Sudan III stain did not reveal the outright bright orange noted in pronounced lipid infiltration, but conveyed the impression of the presence of great amounts of extracellular amorphous material mainly in the upper and middle parts

of the cutis. With the Liebermann-Borchard differential stain for cholesterol these same areas showed a positive staining reaction. Perles' stain for iron-containing pigment revealed no abnormalities.

Course of Illness—For the first four weeks of observation the lesions on the hands, feet, elbows and knees remained stationary. Those on the legs coalesced and spread, finally forming huge painful, necrotic, foul-smelling ulcerations (fig 5), causing the patient to be bedridden. During this period fresh lesions appeared on the ankles and sides of the knees.

On February 15, a diet completely free of animal fat was instituted. After that no new eruption appeared and pain diminished, a tendency toward healing, espe-



Fig 4—Low power microphotograph showing massive cellular infiltrate and absence of foam or giant cells.

cially in the large ulcerated lesions, was noted, with an increased feeling of well-being as shown by the voluntary elimination of sedatives, better appetite and improved morale. A test dose of 100 r applied to an area on the fingers resulted in substantial improvement. The patient also received at various times injections of crude liver extract, high vitamin therapy, thyroid and iron, but without appreciable effect.

DIFFERENTIAL DIAGNOSIS

The most important dermatosis to be considered is, first, xanthomatosis (multiplex tuberosum type). In xanthoma clinically, the lesions

are more yellow and painless, usually lack inflammatory changes and do not ulcerate. Microscopically the intracellular phagocytosis, as evidenced by foam and giant cells and a noninflammatory reaction, are noted. Study of the chemical content of the blood shows hyperlipemia. The rare type, xanthoma areolare multiplex (Riehl and Arzt) is difficult



Fig 5—Photograph showing severity and extent of ulceration

to differentiate clinically from extracellular cholesterosis, but the histologic picture is that of xanthoma.

Eruptions due to halogen drugs can be differentiated only by the characteristic disturbance of lipid in the blood and tissues. At times a history of drug intake is helpful.

With erythema multiforme of comparable severity the patient is febrile, the lesions are not greatly infiltrated, it is more acute and runs a much shorter course. In general, granuloma annulare lesions do not ulcerate, are painless and indolent and have a typical histologic picture.

Idiopathic hemorrhagic sarcoma of Kaposi may simulate extracellular cholesterosis. Absence of lipid deposition, normal blood lipid content, a different histologic appearance and a positive reaction to Perles' stain occur in the former.

COMMENT

As in Urbach's description of extracellular cholesterosis, our patient showed a diminished total lipid and low cholesterol content of the blood serum, increased free cholesterol in the diseased tissue (three times that of a normal control) and a distinctive clinical and histopathologic picture. In Urbach's case the systemic nature of the disease was evidenced by some hepatic insufficiency and splenomegaly, while in our case there was pulmonic involvement, as demonstrated by the physical observations, the roentgenogram of the chest and especially the double refractile bodies and the high cholesterol content in the sputum.

Whereas Urbach showed that ingestion of cholesterol caused an immediate severe exacerbation of the lesions, we found a similar dietary cholesterol relationship by evident and decided improvement in the cutaneous lesions and general condition of the patient soon after she was put on an animal-fat-free diet, which contained practically no cholesterol.

To explain the pathogenesis of the disease, Urbach considered three possible mechanisms. He discarded the first two, namely, (1) a reticuloendothelial cause and (2) an infectious or inflammatory cause. He subscribed to the third theory, that all the features of the disease resulted from a primary disturbance of lipid metabolism. Laymon agreed with this view, as we do also, because our patient was afebrile at all times, there was no adenopathy or splenic involvement, and except for moderate leukocytosis, the hemogram was not indicative of any abnormal state of the reticuloendothelial system. Also, Laymon pointed out the absence of such pronounced lipid changes in any known infectious or inflammatory disease. We would like to note here that inception of the cutaneous condition in our patient occurred during her pregnancy, at a time when there is a known physiologic change in cholesterol metabolism.

Rational speculation along pathogenetic lines as to the cause of this lipid disturbance might well be started here by mentioning an investigation that was done for us by Dr. Herman Sharlit on the patient's blood serum. He corroborated the previous observations of decidedly diminished blood lipid content, including a low cholesterol content. By his special method⁸ he demonstrated *in vitro* that even though there was

⁸ Sharlit, H. The Production and Measurement of Colloid Clouds in Alcoholic Solutions of Blood Serum Lipids, *J. Invest. Dermat.* 5:389 (Dec.) 1942.

present a diminished amount of cholesterol, the blood serum of this patient was unable to absorb appreciable additional amounts of cholesterol as does normal serum, without the lipids breaking out of their emulsified state. This led him to express the belief—especially with our own observation that ingested cholesterol makes the condition clinically worse—that *in vivo*, too, the blood for some reason is unable to hold normal amounts of cholesterol in suspension and it is hence deposited in the tissues. It is the opinion of many investigators that the lecithin and cholesterol ester fractions of the total lipid may have to do with normal cholesterol blood suspension. Thannhauser,⁹ in mentioning the action of the body on cholesterol, pointed out that the liver and circulating blood are important sites for the cholesterase transformation of cholesterol into its esters. Therefore, any disturbance in this enzymatic system would tend to fall in with the previous theoretical consideration. We expect to treat the patient with other lipid fractions, e. g., lecithin orally, to note if there is any effect on the ability of the patient's blood to maintain normal cholesterol suspension.

The next problem is the peculiar histopathogenesis that results when this precipitated cholesterol, after damaging the blood vessel—as so well shown by Urbach—seeps out into the tissues. This is totally different from the picture seen in xanthomatosis, in which there is also a similar deposition of cholesterol in the skin. We can explain this different reaction in extracellular cholesterosis only by the failure on the part of the tissue to metabolize the cholesterol, as in xanthomatosis, setting up instead a severe inflammatory response to a foreign body of irritative and toxic nature.

CONCLUSIONS

A typical example of the disease extracellular cholesterosis as described by Urbach, with the additional systemic feature of pulmonic involvement, is described.

As done previously only in Urbach's exhaustive studies, chemical determinations of skin cholesterol were carried out and are reported.

We have suggested the two possible causes for the clinical symptoms, namely (a) an inability of the blood to sustain normal levels of cholesterol and (b) an unusual inflammatory response of the skin to the cholesterol deposited in the tissues as a result of the aforementioned failure.

This is a preliminary report. Further experimentation is being undertaken to find out the factors which cause such cholesterol precipitation and studies made of the response of normal and diseased animal and human skin to the introduction of cholesterol intradermally.

Dr. M. Bruger and Miss E. Goldman of the Department of Chemistry, New York Post-Graduate Hospital, gave assistance in this work.

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LEUKODERMA PRODUCED BY ANTIOXIDANTS

Report of Cases

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THE PURPOSE of this paper is to present additional cases of leukoderma produced by antioxidizing agents contained in manufactured articles. The chemistry of rubber and rubberized industries has developed not only along lines of greater production of synthetic products but also toward extending the aging of these goods. For this latter objective, the chemical compound "agarite alba," the trade name for monobenzyl ether of hydroquinone, an antioxidant of pigment, is usually added. This observation was first established by Oliver, Schwartz and Warren.¹ These authors observed in the tanning industry occupational leukoderma in men wearing rubber gloves which contained this antioxidant to help the aging of rubber. Another observation was made of occupational leukoderma in a woman employed to wash contraceptive diaphragms in a gynecologic laboratory.²

REPORT OF CASES

CASE 1—E. B., a man aged 29, consulted me because of the appearance of white patches on the hands. These had been increasing in size and number for the two months prior to examination. He was employed by a firm the business of which was to cover metal objects with a rubber compound. His particular duties were to immerse wire dish tray holders into this compound. He had been doing this for about two years, but only for two or three months prior to examination had he noticed the appearance of white spots on his hands. The only discomfort experienced was a warm feeling in his hands in the evening, after work. This feeling, he stated, did not occur over the week end, when he did not work.

Examination showed absence of pigment in patches involving the fingers of both hands (fig. 1). This was especially noticeable on and between the fifth, fourth, third and index fingers. On the dorsum of the hands there were a few discrete pinhead-sized to pea-sized leukodermic macules. There were no erythematous or scaling lesions noticeable. Also on the forearms there were a few pea-sized leukodermic spots. A patch test performed on the arm with the rubber compound and left in place for four days gave a positive result, in that a small pea-sized leukodermic spot was observed. The particular firm in question gave the

1 Oliver, E. A., Schwartz, L., and Warren, L. H. Occupational Leukoderma, *Arch. Dermat. & Syph.* **42** 993 (Dec.) 1940.

2 Spencer, G. A. Pigmentogenesis, *J. Nat. M. A.* **36** 43, 1944.

information that for the past three months 1 per cent of the chemical agent "agarite alba" had been added to the rubber compound. The rest of the examination revealed nothing abnormal.



Fig 1—Leukoderma involving fingers of both hands



Fig 2—Discrete leukodermic spots on and between the fingers

CASE 2—B B, a man aged 26, brother to E B, consulted me at the same time for a similar absence of pigment on the hands. He noticed the condition of his hands for three months. He was also employed by the same firm, and his special



Fig 3—Rectangular leukodermic area on the side of face



Fig 4—Leukodermic area on the inner aspect of the leg and the foot

duties were to take the dipped trays from his brother and to wash them in water. In his case there were no subjective symptoms.

Examination showed discrete pinhead-sized to pea-sized leukodermic spots on the dorsal surface of both hands. A few such spots were seen in the webs of the fingers (fig 2). Also, on the glans penis there was a pea-sized spot, probably a self-imposed patch test. No erythematous or scaling lesions were noticeable. A patch test of the compound, performed on the arm and left for four days, gave a positive result, in that a small pea-sized leukodermic spot was observed.

CASE 3—A woman aged 30 was seen by me for absence of pigment which had appeared on the face and on the left leg. She stated that she had been hospitalized for an acute infection of the upper part of the respiratory tract and a sprained left ankle. During her stay of three weeks in the institution, her ankle was strapped



Fig 5—Bandlike leukoderma on the forehead, corresponding to contact of the hat band.

with adhesive tape and oxygen therapy was administered for the pulmonary condition. The nasal catheters were kept in place for a few days by means of adhesive tape. On returning home she noticed the condition of her face and ankle.

Examination showed leukodermic areas on both sides of the face. On the right side there were two well defined patches devoid of pigment, each about 4 inches (10 cm) in length and $\frac{1}{2}$ inch (1.3 cm) in width. One of these patches was rectangular in shape (fig 3). On the inner aspect of the left leg there was a well defined almost rectangular area of leukoderma, about 10 inches (25 cm) in length, extending from the arch over the external malleolus and up to the inner aspect of the left leg (fig 4). The rest of the body showed nothing abnormal. A patch test performed with adhesive tape and left in place for four days gave a positive result with a leukodermic area corresponding to the size and shape of the patch. It was not possible to learn the nature of the antioxidant used in the manufacture of the tape.

CASE 4—A G, a man aged 40, a postal employee, was seen by me for an eruption involving the forehead and scalp (fig 5) He stated that he had bought a regulation cap and after wearing the cap for a week experienced a slight burning sensation of the scalp

Examination showed leukodermic areas on the forehead and in the parietal and occipital regions of the scalp corresponding to the contact with the band of the cap A patch test performed with a piece of the band and left in place for four days gave a positive reaction with a leukodermic area The band consisted of compressed paper that was processed It was not possible to ascertain the exact chemical constituents of the compound

SUMMARY

Cases of leukoderma produced by antioxiðizing agents are reported One such antioxiðizing agent is "agarite alba," trade name for monobenzyl ether of hydroquinone

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ACUTE RECURRENT PUSTULAR BACTERID

Report of a Case

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AS EARLY as 1920, Bloch stated his belief in the existence of secondary eruptions from foci of infections produced by many different types of micro-organisms and he suggested the inclusive name "microbids" for such eruptions, whether due to cocci, fungi, viruses or other infectious agents

Later, in 1934, Andrews, Birkman and Kelly¹ described a group of "recalcitrant pustular eruptions of the palms and soles" in 15 patients and differentiated them from similar eruptions by certain criteria. Andrews and Machacek,² in 1935, confirmed and expanded the preceding report. In a third paper, in 1941, Andrews and Barnes³ analyzed 200 cases of recalcitrant eruptions of the palms and soles and found twenty-four "pustular bacterids" among them. Finally, in the latest edition of his textbook (1946)⁴ Andrews gave the most recent résumé of the pustular bacterid.

According to these descriptions the eruption is of a chronic character with acute exacerbations, sometimes lasting for many years, beginning with vesicles and pustules in the middle portions of the palms and soles and soon extending outward, especially to the lateral surfaces. If there are vesicles they soon become pustular and hemorrhagic puncta also become visible. In the later stages some crusting and characteristic adherent scaling develop. The lesions are sometimes unilateral, usually, however, they break out symmetrically, or successive crops show symmetric distribution. They heal by drying up and scaling off. Their differential diagnostic characteristics are (1) culturally sterile pus (in contrast to Hallopeau's acrodermatitis continua and to dermatitis repens as well as to dermatophytosis, secondarily infected dyshidrosis, pompholyx and vesiculopustular dermatitides), (2) almost always

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1 Andrews, G C, Birkman, F W, and Kelly, R J. Recalcitrant Pustular Eruptions of Palms and Soles, *Arch Dermat & Syph* **29** 548-563 (April) 1934

2 Andrews, G C, and Machacek, G F. Pustular Bacterids of the Hands and Feet, *Arch Dermat & Syph* **32** 837-847 (Dec) 1935

3 Andrews, G C, and Barnes, M C. Pustular Bacterids and Allied Conditions, *South M J* **34** 1260-1266 (Dec) 1941

4 Andrews, G C. Diseases of the Skin, ed 3, Philadelphia, W B Saunders Company, 1946, pp 262-264

detectable infectious foci, usually abscessed tonsils, sometimes infected teeth, the removal of which is followed by healing of the eruption, which otherwise is recalcitrant to all treatment, (3) characteristic histologic changes (deep-seated epidermal pustules with acanthosis) that differentiate the disease from psoriasis, the existence of which should be excluded, and (4) positive allergic cutaneous reactions with vaccines from pyogens



Fig 1—Vesiculopustular and hemorrhagic eruption of the palms and wrists

If these criteria are applied strictly, then the pustular bacterid is uncommon. The following case is, in my opinion, a good example of the disease.

REPORT OF A CASE

R K, a 27 year old white veteran, was admitted to the hospital on May 19, 1946. His previous history was essentially noncontributory. In the previous seven months he had had three or four attacks of acute tonsillitis, and simultaneously there developed "blisters" on the feet, ankles, legs, knees and hands. After the tonsillitis had subsided the cutaneous lesions dried up and healed within about one week.

Ten days before admission a sore throat recurred. Three days later lesions began to break out on the palms and soles.

On admission the patient had a temperature of 102.4 F. Both tonsils were moderately enlarged and reddened, and showed a number of small follicular abscesses. The regional submaxillary lymph nodes were distinctly palpable, rather soft

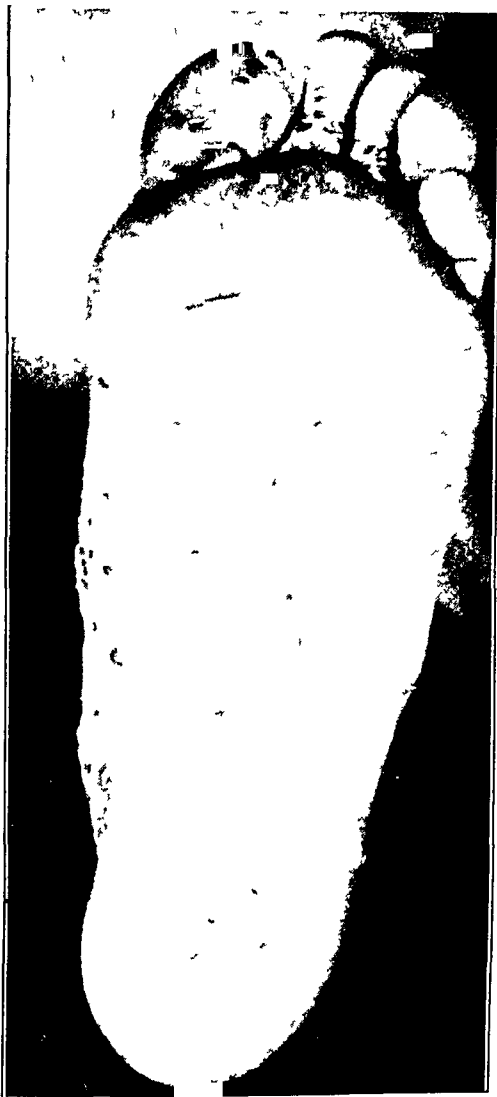


Fig. 2—Vesiculopustular and hemorrhagic eruption of the left sole and of the toes

and somewhat tender. There were no other abnormal physical observations excepting the rash.

The patient presented a generalized eruption of vesiculopustular and hemorrhagic character (figs. 1 and 2). The skin of the arches and the adjacent medial surfaces of the feet, the middle portions and the thenar eminences of the palms and the volar aspects of the wrists were studded with numerous discrete lesions, most of which were pustular. Lesions of the same kind also appeared on the plantar sur-

taces of the toes, a few on the volar and lateral sides of the fingers, some more on the legs, and scattered vesicles and pustules on the thighs, on the upper extremities and on the entire trunk. The scalp, face and neck were free of lesions. There was no lymphangitis or lymphadenitis.

The white blood cell count showed 14,200 leukocytes, with 72 per cent neutrophils. The red cell count and the urine were normal. The Kahn reaction was negative.

Direct examination of the pus and vesicle fluid from the cutaneous lesions revealed no mycelia or spores, and there were none in the tops of the vesicles from the toes. Repeated examinations were made. Cultures on Sabouraud's agar remained sterile. Gram stains for bacteria gave likewise negative results, and cultures for pyogenic organisms produced no colonies. However, hemolytic streptococci could be seen in stained smears, and grew in cultures, from the pus of the abscessed tonsils.

In the first few days the patient received potassium permanganate baths and the hands and feet were soaked in solution of aluminum acetate. After the laboratory observations had been obtained, on May 27, the patient took 1 Gm of sulfadiazine six times a day for four days (initial dose 2 Gm). During this time the throat infection cleared up and the cutaneous lesions began to dry, there developed some crusting and scaling, and within about one week after the beginning of the treatment with sulfonamide drugs there was only slight scaling left. No new lesions had developed after the start of sulfadiazine therapy.

Then a tonsillectomy was advised by the eye, ear, nose and throat section, and the patient promised to have this operation performed within the next few weeks. Unfortunately contact with him was lost after his discharge from the hospital.

COMMENT

The simultaneous occurrence of the streptococcic tonsillitis and the cutaneous eruption, the sterility of the cutaneous lesions and the prompt healing of the rash coincident with the spontaneous regression of the sore throat or after sulfadiazine therapy, all were factors that made the case unusually interesting. It is to be regretted that permanent cure after tonsillectomy was not observed because the patient was lost to observation after he left the hospital. Such a result could have been confirmatory evidence of Andrews' concept. However, the case seems clear enough, even without the "crucial test," and it might, therefore, contribute to the recognition of the dermatosis.

SUMMARY

A 27 year old white man showed repeated streptococcic sore throats and simultaneous vesiculopustular eruptions of the palms and soles. Bacteriologic and fungus examinations including cultures, of the cutaneous lesions showed negative results. The cutaneous rash healed spontaneously after the regression of the tonsillitis after sulfadiazine therapy. The case may serve as evidence for the existence of the "pustular bacterid."

VIOFORM IN DERMATOLOGIC THERAPY

With Particular Reference to Its Use in Different Vehicles

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THE QUINOLINE derivative known as "vioform" (5-chloro-7-iodo-8-hydroxyquinoline) has been extensively used internally for the treatment of amebic dysentery. Although European dermatologists¹ have long recognized the value of "vioform" in the external treatment of skin diseases, the usefulness of this compound in external dermatologic therapy has not yet received full recognition in the United States. Only a few references² can be found in the literature of this country. It was not until 1944 that the "New and Nonofficial Remedies" of the Council on Pharmacy and Chemistry of the American Medical Association included the mention of the external therapeutic use of "vioform".³

The mode of "vioform's" therapeutic action is not known, and the indications and value of the drug have been established almost exclusively on an empiric foundation.

Subsequent to the completion of the present report a note on the use of "vioform" in local therapy appeared in *THE ARCHIVES* (Saunders, Thomas S. The Use of Vioform in Local Dermatologic Therapy, *Arch Dermat & Syph* 54:456 [Oct.] 1946). The publication of Saunders' note impels us once more to call attention to the fact that the usefulness of vioform in external treatment is not a notion on our part, but is founded on many decades of experience on the part of a great number of competent dermatologists and is based on observations in at least tens of thousands, and probably hundreds of thousands, of cases. While differences of opinion not only "make hoss racin'" but often also make for progress in medicine, it seems regrettable that a publication should appear in which a dissenting opinion is based on only 14 cases. Perhaps if Dr. Saunders had had more experience or if more details of Dr. Saunders' experience were available, it would be possible to discover the causes for his unfavorable impressions.

1 Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Vol. V/1, Berlin, Julius Springer, 1930, vol. 5, pt. 1.

2 Wise, F., and Sulzberger, M. B. *Year Book of Dermatology and Syphilology*, Chicago, Ill., The Year Book Publishers, Inc., 1942. Sulzberger, M. B., and Wolf, J. *Dermatologic Therapy in General Practice*, *ibid*, 1942. Pillsbury, D. M., Sulzberger, M. B., and Livingood, C. S. *Manual of Dermatology*, Philadelphia, W. B. Saunders Company, 1942.

3 *New and Non-Official Remedies*, Chicago, American Medical Association, 1944.

Based on personal experience which extends over twenty years and on direct observations which include several thousand cases, we believe that the most important indications for the external application of "vioform"-containing preparations are as follows

1 Dermatoses and infections in which a mild antibacterial and antifungous effect is desired and in which irritant action must be reduced to an absolute minimum (paronychias, secondarily infected herpes simplex, erosio interdigitalis, impetigos), i e, dermatoses due to superficial infections or which have been irritated by previous therapy or by other factors and in which other local antiseptic agents, such as mercury, resorcinol, iodine, penicillin and sulfonamide drugs, are contraindicated, not tolerated or not effective

2 Eczematous eruptions in acute, subacute or chronic stages, and particularly in nummular eczemas, in impetiginized or infected eczemas of the hands or other parts and in eczematized superficial infections In these conditions the "vioform" application can be used alternately with soothing and antiseptic and antieczematous wet compresses, tinctures or lotions or can replace these when they are not feasible, not effective or not tolerated

3 Atopic dermatitis, when other commonly used agents have failed or have caused aggravation and particularly in areas with eczematization and superficial infection due to scratching or other causes

4 Psoriasis, particularly in irritated and pruritic areas and areas with secondary superficial dermatitis, maceration and eczematization, for example, psoriasis of the genitalia, intergluteal, scrotal and inverse psoriasis, eczematized psoriasis of such areas as the ears, hands or feet, or cases in which other antipsoriatic remedies are not tolerated or not beneficial

5 Seborrheic dermatitis, here the indications are similar to those in psoriasis, i e, when conditions such as superficial irritation and eczematization or maceration are present, in intertriginous sites, and when other conventional remedies irritate

6 In pruritus ani, pruritus vulvae and other such pruritic conditions, when superficial infection, maceration and irritation play a role or when other remedies are ineffective or irritating

7 Sycosis vulgaris, particularly when irritability, erythema or seborrheic features are an important part of the picture and eczematization, redness and greasy scaling are present in addition to the classic infected follicular lesions

8 As a soothing and antiseptic application whenever a remedy is desired which is likely to be less irritating than other combinations of antiseptic and antiphlogistic agents

The employment of "vioform" preparations in any of the aforementioned conditions does not preclude the concomitant use of other remedies. On the contrary, it is often desirable or necessary to employ such combined therapy as hot wet compresses or soaks with potassium permanganate several hours daily and "vioform" applications the remaining time or tinctures (such as Arning's tincture [anthrarobin, tumenol, ether and tincture of benzoin]) during the day and "vioform" applications at night.

In Europe the most commonly employed "vioform" preparation was an ointment consisting of 5 per cent "vioform" in petrolatum. This was applied and usually kept on under carefully fitted smooth linen or cotton bandages. One of us (M. B. S.) can recall no case of severe irritation and only a few of sensitization among the large series of patients in which this preparation was employed in Switzerland and Germany. On returning to the United States in 1929, one of us (M. B. S.) found that the 5 per cent concentration of "vioform" in petrolatum was apparently well tolerated here, also, until about the end of the year 1940. From that time on, occasional instances of irritation and sensitization were observed.

In an effort to establish the reasons for this change, it was learned that the manufacture of "vioform" in the United States had been started in May 1940 and that the process as used here yielded a finer lighter powder with smaller particle sizes than the product formerly imported from Switzerland. On the assumption that this difference in physical properties would achieve a greater surface effect and would be more active per unit of weight, we lowered our routine concentration in petrolatum from 5 per cent to 3 per cent and sometimes, even to 2 per cent or less. Thereafter the incidence of sensitizations again became negligible, "vioform" preparations having the lowered concentration are less sensitizing than most other antiseptics in common use (sulfonamide drugs, penicillin, mercurials, other quinoline derivatives). Nevertheless, rare cases of irritation or sensitization have occurred, and it is our impression that their incidence may be slightly higher here than in Europe.

While "vioform" in white petrolatum is to date by far our most commonly employed preparation, we have used "vioform" in shake lotions (e. g. zinc oxide, talc, glycerin, alcohol, water), in emulsions (e. g. calamine liniment N. F.), as a powder in talc and in other forms and vehicles.

"VIOFORM" IN WATER-WASHABLE CREAM

"Vioform" 3 per cent in white petrolatum makes a brownish rather soft ointment which requires bandaging and which tends to produce yellowish staining of materials and of the surface of the skin. For these reasons, it seemed to us desirable to attempt to use "vioform" in a water-washable vanishing cream type vehicle which would not be so greasy, would not require bandaging and which might reduce the staining.

properties of "vioform" For several years we studied the effects of "vioform" in 3 per cent concentration in a number of different oil-in-water emulsion cream vehicles Although several acceptable creams were obtained, these preparations appeared to be more irritating than the same concentration of "vioform" in petrolatum

In June 1945, we started to use a new preparation of "vioform" 3 per cent in a water-washable cream⁴ The vehicle used in this cream consists of

Sodium lauryl sulfonate
Stearyl alcohol
Spermaceti
Glycerin
Petrolatum, yellow
Distilled water

One of the principal differences between this water-washable cream and those previously tried by us is that this cream is especially milled after the "vioform" has been added to the vehicle This specially prepared and milled cream has now been used by us in a relatively large series of cases Table 1 enumerates those cases encountered in our practice which could be followed sufficiently carefully and over a long enough period of time to permit an evaluation of effects

TABLE 1—Cases Studied

Condition	No of Cases
Eczematous dermatitis, including secondarily infected cases (allergic and non allergic eczematous dermatitis, dermatophytids, nummular eczemas, etc)	55
Atopic dermatitis	24
Miscellaneous dermatoses (exfoliative erythroderma, pyoderma, intertrigo, etc)	9
Psoriasis	8
Seborrheic dermatitis	6

Table 2 presents the results obtained in these 102 cases

TABLE 2—Effect of "Vioform" 3 per Cent in Water-Washable Cream in 102 Cases

Diagnosis	Total Number of Cases	Number of Cases with Good* Results	Number of Cases with Fair† Results	Number of Cases with Poor‡ Results	Number of Cases in Which Irritation Was Noted	Number of Cases in Which Sensitization Was Noted
Eczematous dermatitis	55	28	15	12	7	
Atopic dermatitis	24	13	7	4	3	
Miscellaneous dermatoses	9		5	4	2	
Psoriasis	8	4	4			
Seborrheic dermatitis	6	4		2		

* Good results The cream had a major share in bringing about healing of the eruption
† Fair results The cream brought improvement but was combined with or followed with other remedies in order to bring about final healing
‡ Poor results The cream did not bring about any improvement, the dermatosis remaining unchanged or getting worse

⁴ The Ciba Pharmaceutical Co., Summit, N. J., supplied us with the Vioform cream used in this study

SIDE EFFECTS OF "VIOFORM" PREPARATIONS

Primary Irritancy and Sensitization—On "normal" skin "vioform" 3 per cent entirely lacks primary irritancy when applied in any of the various vehicles mentioned in the present report. As previously stated, the incidence of irritations and of sensitizations from the therapeutic use of "vioform" 3 per cent in petrolatum is low as compared with other commonly used dermatologic remedies. Table 2 shows that there were no cases of sensitization due to "vioform" among the 102 cases in the series treated with the 3 per cent preparation in the water-washable cream. We believe that these results indicate that the sensitizing index of this preparation is sufficiently low to compare favorably with that of "vioform" 3 per cent in petrolatum.

Incompatibilities—"Vioform" can be combined with or used on areas previously treated with most of the commonly used topical agents, with the possible exception of mercury and sulfur. However, we do not recall observing any irritations after using the preparation on areas which twenty-four to forty-eight hours previously had been treated with mercury or sulfur. Still, it is theoretically possible that the small quantities of free iodine liberated by "vioform" might form irritating compounds with mercury and sulfur. Therefore, we believe that it is wise to let at least one day intervene between the successive use of "vioform" and mercury or sulfur on the same cutaneous area.

Systemic Toxicity The fact that "vioform" is safely administered by mouth and in the form of vaginal suppositories clearly indicates that under the usual conditions of dermatologic use there is no reason to fear toxic manifestations due to absorption. This point of view is supported by the lack of reports on systemic toxicity of the preparation after topical use and by the relatively low degree of toxicity observed in the pharmacologic studies of David, Phatak and Zener.⁵ However, because of the possible rise of the iodine level in the blood after absorption of "vioform," the use of this drug over large areas may be contraindicated in some cases of iododermas and in dermatoses commonly associated with hypersensitivity to iodides, such as dermatitis herpetiformis, bromodermas or acne vulgaris.

COMMENT

In submitting these impressions of "vioform" in old and new vehicles we are fully aware that the correct and speedy evaluation of topical remedies for dermatologic therapy on the clinical material of a private practice or of a clinic is a difficult matter. A really scientific evaluation is often almost impossible, mainly because of the variability of response in

5 David, N. A., Phatak, N. M., and Zener, F. B. Iodochlorhydroxyquinoline and Di-Iodo-hydroxyquinoline. Animal Toxicity and Absorption in Man, *Am J Trop Med* 24:29, 1944.

different cases or even different areas of the same dermatosis. For this reason it is usually impossible to compare the effects of a new remedy with those of an established "standard" treatment agent without employing almost astronomic numbers of cases in order to rule out chance variations. An evaluation of two treatment agents through their comparison on similarly affected symmetrically situated sites in the same persons has been employed by us for many years as perhaps the closest possible practical approach to a scientific study of topical treatment agents. Confirmatory work in this direction has been carried on independently by Siemens,⁶ who refers to previous work on this method by Schweninger, Unna, Dreuw and Schaffer.

Although this fact could not be included in table 2, in many of our cases we have employed this method of paired comparison.⁷ The results of such comparison of "vioform" preparations with other treatment agents and with the vehicle alone used on symmetrically situated similarly affected sites indicated that the drug is an effective and often superior treatment agent.

Despite the excellent impressions gained from our own evaluations and despite the decades of favorable clinical experience with "vioform" in white petrolatum, we by no means intend to imply that "vioform" is always an effective topical remedy, but only that it is another valuable agent to be included in the dermatologic armamentarium. In our experience the value of "vioform" in topical therapy ranges with that of such proved remedies as the tars, mercury, sulfur and resorcinol.

The choice of the vehicle in which "vioform" should be used in any particular case or area must be based on considerations similar to those governing the choice of the vehicle for other topically used agents. As previously stated, "vioform" 3 per cent in petrolatum is in general the most widely employed and useful "vioform" preparation, and the "vioform" in water-washable cream, while it has special indications, can by no means replace the more greasy preparation which is indicated in the many cases in which softening and occlusive effects and protective bandaging are desired. However, in the present report we wish to call attention to one mode of use which was found to be effective and particularly practical in a fairly large number of cases. In these cases, "vioform" 3 per cent in the water-washable cream was used during the day and "vioform" 3 per cent in petrolatum at night. This combination permits treatment during the day with "vioform" in a nonocclusive and relatively nonmessy form, which does not necessitate bandaging, and during the

6 Siemens, H. W. Die Leistungsfähigkeit der Einseitenbehandlung in der experimentellen dermatologischen Therapie, Arch Dermat u Syph **183**:223, 1942.

7 Sulzberger, M. B., Baer, R. L., Kanof, A., and Lowenberg, C. Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin, J Invest Dermat **7**:227, 1946.

might with "vioform" in a more lubricating and occlusive form, which can easily be carried out under bandages, white cotton gloves or socks, whichever the case may require

SUMMARY AND CONCLUSIONS

Both long clinical experience and the present studies indicate that "vioform" (5-chloro-7-iodo-8-hydroxyquinoline) is a valuable remedy in topical therapy. It is effective as well as relatively nonirritating and nontoxic and has a low sensitizing index. The principal indications for the dermatologic use of "vioform" preparations are selected cases of eczematous dermatitis, atopic dermatitis, bacterial and mycotic dermatoses, psoriasis, seborrheic dermatitis, sycosis vulgaris and other infected and irritated lesions.

The preparation can be employed topically in various vehicles. In our experience a petrolatum base and a special water-washable cream have been the two most effective and practical vehicles. In 102 consecutive cases in which the effects of "vioform" 3 per cent in the special water-washable cream could be adequately evaluated, the clinical effects were considered good in 49, fair in 31 and poor in 32.

ADDENDUM

Since submitting this report we have confirmed our observations in hundreds of additional cases. The results have strengthened our conviction that "vioform" preparations, while not panaceas, are among the most valuable local therapeutic agents with very low irritancy and a low index or potential of sensitization.

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TREATMENT OF PITYRIASIS ROSEA WITH NONSPECIFIC SUBSTANCES

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THIS REPORT is based on the observation and treatment of 270 patients suffering from pityriasis rosea. Injections of fungus extracts, staphylococcus toxoid and a sterile solution of lactalbumin in colloidal form were the therapeutic agents used, with isotonic sodium chloride solution U S P as the control. These studies were started in and carried on from 1943.

Pityriasis rosea was first described as a separate entity by Gibert¹ in 1860. Since then numerous attempts were made to discover the cause with its resultant specific therapy. A great variety of observations have been published as to causation. A brief summary of these various concepts follows.

Many authors have expressed a belief in the infectious origin of pityriasis rosea. Vidal² in 1882 was the first to describe the presence of an organism in the scales, which he named *Microsporon dispar*. Brocq,³ his pupil, described the initial plaque as such and stated that it might be caused by an unknown infectious agent, transmitted by flea bites. In 1893 Kaposi⁴ discovered mycelia, in 1912 DuBois⁵ found "microspora" in the scales of pityriasis rosea. Later Gougerot⁶ saw spores in them, as did Photinos,⁷ Covisa,⁸ Joyeux,

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post-Graduate Medical School and Hospital (Dr Marion B. Sulzberger, Director)

1 Gibert, C. M. *Traite pratique des maladies de la peau et de la syphilis*, ed 3, Paris, H. Plon, 1860, vol 1, p 402.

2 Vidal, E. *Du pityriasis circine et marginé*. Description de son myco-derme, le *microsporon anomoeon* (*microsporon dispar*), *Ann de dermat et syph* 3 22 (Jan) 1882.

3 Brocq, L. *Note sur la plaque primitive du pityriasis rose de Gibert*, *Ann de dermat et syph* 8 615 (Oct) 1887.

4 Kaposi, M. K. *Lehrbuch der Hautkrankheiten*, Vienna, 1893.

5 Du Bois. *Parasite cryptogamique des dermatoses érythémato-squameuses du type pityriasis rose de Gibert*, *Ann de dermat et syph* 3 32 (Jan) 1912.

6 Gougerot, H. *Traitement du pityriasis rosé de Gibert par l'éosine*, *Bull Soc franc de dermat et syph* 44 1708 (July) 1937.

7 Photinos, P. *Beitrag zur Natur der Pityriasis rosea*, *Dermat Ztschr* 68 187 (Jan) 1934, abstracted, Wise, F., and Sulzberger, M. B. *Year Book of Dermatology and Syphilology*, Chicago, The Year Book Publishers, Inc., 1934, p 565.

(Footnotes continued on next page)

Burnier and Duche⁹ Oppenheim¹⁰ discovered oidium-like organisms in the herald patch and stated that the secondary lesions were probably produced by emboli of these organisms in the fine capillaries of the skin. Highman and Rulison¹¹ stated that pityriasis rosea, in their belief, was caused by an external infectious agent, the portal of entry of which was the herald spot. Gori and Voigt¹² stated the belief that pityriasis rosea was caused by *Staphylococcus pyogenus albus*. Wile¹³ was able to produce an eruption similar to pityriasis rosea by transmission. Simon¹⁴ and Thomson and Cumings¹⁵ stated that pityriasis rosea was caused by a filtrable virus. Benedek¹⁶ attributed pityriasis rosea to a constant endoparasite, which produces the eruption by hematogenous spread.

Lassar,¹⁷ J. Jadassohn,¹⁸ Veiel,¹⁹ Wise and Sulzberger²⁰ and Pick²¹ stated that pityriasis rosea in many cases followed shortly after the wearing of new, stored or humid clothing. MacKee,²² Kogoj and

8 Covisa, S. Pityriasis rosea. *Gibert, Dermat Wchnschr* **56** 115 (Jan 25) 1913

9 Joyeux, Burnier and Duche. Recherches sur la nature mycosique du pityriasis rose. *Bull Soc franç de dermat et syph* **37** 1128 (July 10) 1930

10 Oppenheim, M. Ueber Pityriasis rosea, *Verhandl Gesellsch d deutsch Naturforsch u Arzte* **79** (pt 2) 409, 1907, abstracted, *Arch f Dermat u Syph* **88** 355, 1907

11 Highman, W. J., and Rulison, R. H. Pityriasis Rosea. A Few Simple Facts, *Arch Dermat & Syph* **7** 163 (Feb) 1923

12 Gori, L., and Voigt, L. Zur Aetiologie der Pityriasis rosea, *Munchen med Wchnschr* **71** 599 (May 2) 1924

13 Wile, U. J. Experimental Transmission of Pityriasis Rosea. Preliminary Report, *Arch Dermat & Syph* **16** 185 (Aug) 1927

14 Simon, C. Quelques reflexions et souvenirs sur le pityriasis rose de Gibert, *Bull med, Paris* **50** 702 (Oct 24) 1936

15 Thomson, M. S., and Cumings, J. N. Investigations into the Causation of Pityriasis Rosea, *Brit J Dermat* **43** 617 (Dec) 1931

16 Benedek, T. Syphilis and the Biotropic Skin Exanthems of Known Bacterial Hematogen-Endogenous Origin, Seborrheic Dermatitis, Pompholyx, Pityriasis Rosea, Psoriasis Vulgaris, *Urol & Cutan Rev* **46** 409 (July) 1942, Schizosaccharomycosis II Clinical (Mycide) Forms, Pityriasis Rosea of Gibert, Its Etiology and Pathogenesis, *Arch Dermat & Syph* **26** 397 (Sept) 1932

17 Lassar, O. Ueber die Natur der Pityriasis rosea, *Deutsche med Wchnschr* **18** 469 (May 26) 1892

18 Jadassohn, J., in Darier, J. *Grundriss der Dermatologie*, translated by K. G. Zwick, Berlin, Julius Springer, 1913, p 66

19 Veiel, F. Zur Kenntnis der Pityriasis rosea, *Dermat Ztschr* **62** 91 (Sept) 1931, abstracted, Wise, F., and Sulzberger, M. B. *Year Book of Dermatology and Syphilology*, Chicago, The Year Book Publishers, Inc., 1931, p 153

20 Wise, F., and Sulzberger, M. B. Editorial comment on Veiel¹⁹, Editorial comment on Photinos⁷

21 Pick, E., in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1928, vol 7, pt 1, p 401

22 MacKee, G. M. Personal communication to the author

Farkas,²³ Moingeard,²⁴ Thibierge,²⁵ Fox,²⁶ Pollitzer,²⁷ Pusey,²⁸ Kyrle,²⁹ Chevallier³⁰ and Wile³¹ stated that pityriasis rosea behaved like the infectious exanthemas and belonged to that group. Feulard,³¹ Szabóky³² and Jaquet³³ expressed the belief that pityriasis rosea was of gastrointestinal origin. Hyde,³⁴ Alderson,³⁵ Szabóky³² and Jaquet³³ observed that some of the cases of pityriasis rosea had a psychogenic or neurogenic background. Owens,³⁶ Little,³⁷ Mestchersky,³⁸ Haspel,³⁹ Hazen,⁴⁰ Pernet,⁴¹ Dore⁴² and MacLeod⁴³ saw cases in which the disease was preceded by, or associated with, tonsillitis. Le Damany⁴⁴ classed pityriasis rosea with the tuberculids.

23 Kogoj, F, and Farkas, K. Clinical Contribution on Pityriasis Rosea, *Urol & Cutan Rev* **36** 451 (July) 1932

24 Moingeard, A. Etude sur le pityriasis rose de Gibert, Thesis, Paris, no 325, 1889

25 Thibierge, G. Pityriasis rose, in Besmer, E., Brocq, L., and Jaquet, L. *La Pratique dermatologique*, Paris, Masson & Cie, 1900, vol 3, p 873

26 Fox, G H. A Broader View of Pityriasis Rosea, *J A M A* **59** 493 (Aug 17) 1912

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29 Kyrle, J. Vorlesungen über Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925-1927, vol 1, p 178

30 Chevallier, P. Une maladie souvent confondue avec la roseole syphilitique, le pityriasis rosé de Gibert, *Hôpital* **12** 661, 1924

31 Feulard, H. Pityriasis rosé de Gibert, dilatation de l'estomac, *Ann de dermat et syph* **10** 459 (May 25) 1889

32 Szabóky, J. Beiträge zur Ätiologie der Pityriasis rosea, *Monatsh f prakt Dermat* **42** 495 (May 15) 1906

33 Jaquet, cited by Pick²¹

34 Hyde, cited by Alderson³⁵

35 Alderson, H E. Pityriasis Rosea. Clinical Observations, *J Cutan Dis* **32** 353 (May) 1914

36 Owens, W D. Observations on Pityriasis Rosea, *J Cutan Dis* **32** 347 (May) 1914

37 Little, E G G. Discussion on Pityriasis Rosea, *Proc Roy Soc Med* **7** 121 (March) 1914

38 Mestchersky, G. Contribution à l'étiologie du pityriasis rose de Gibert, *Bull Soc franç de dermat et syph* **33** 148 (Feb 11) 1926

39 Haspel, K L. Angaben zur Ätiologie der pityriasis rosea, *Dermat Wchnschr* **102** 357 (March 21) 1936

40 Hazen, H H. Late Observations on the Etiology and Treatment of Pityriasis Rosea, *South M J* **24** 937 (Nov) 1931

41 Pernet, G, in discussion on Little³⁷

42 Dore, S E, in discussion on Little³⁷

43 MacLeod J M H, in discussion on Little³⁷

44 Le Damany, P. Le pityriasis rose de Gibert est une tuberculide, *Presse med* **27** 121 (March 10) 1919

This large variety of theories led to varied therapeutic experiments. Besides treatment of pityriasis rosea with diverse topical remedies and physical agents, numerous attempts were made to treat it by means of parenteral methods.

Leiner⁴⁵ gave his patients intramuscular injections of milk Stillians and Benedek administered intradermal injections of Benedek's vaccine. Gurvich⁴⁶ used subcutaneous injections of a streptococcus vaccine. Fidanza, Carrillo and Schujman⁴⁷ reported the intravenous use of a streptococcus vaccine. Niles and Klumpp⁴⁸ treated their patients with convalescent serum. Ebert and Otsuka⁴⁹ used typhoid vaccine by intramuscular route.

EXPERIMENTAL STUDIES

My patients ranged from 2 to 66 years of age, the average being 35 years. One hundred and fifty-one were female, 119 were male.

One hundred and seventy-seven of the patients had one herald patch, 16 patients had multiple herald patches, and 77 patients had none which were recognizable as such. Ninety patients suffered from itching. The face was involved in 39 patients, the neck in 80 and the scalp in 18. One patient had lesions of the oral mucosa (the Wassermann and Kahn reactions being negative). Six patients had cervical adenitis. The duration of the eruption when first observed varied between one and twenty weeks, the average being ten days. Eighty-one patients stated that they had worn new, stored or humid clothing within a short period before onset of the eruption. Forty-two had had gastrointestinal disturbances before or during the appearance of the pityriasis rosea lesions. Thirty-two gave a history of nervous upsets preceding or accompanying the disease. Two patients had pityriasis rosea for the second time within three years. These patients were treated in four groups.

Group 1—Because the picture of pityriasis rosea is one often seen in dermatoses caused by fungi, I assumed that pityriasis rosea might be of fungous origin and decided to treat patients suffering from it with fungous extracts.

45 Leiner, C. Zur Behandlung der Pityriasis rosea im Kindesalter mit Milch-injektionen, *Wien med Wchnschr* **71** 1802 (Oct 15) 1921.

46 Gurvich, E. I. Sur la clinique, la pathogenie et le traitement du pityriasis rose de Gibert. Pityriasis rosea Gibert, *Ann de dermat et syph* **7** 488 (May) 1936.

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48 Niles, H. D., and Klumpp, M. M. Pityriasis Rosea. Review of the Literature and Report of Two Hundred and Nineteen Cases, in Thirty-Eight of Which Convalescent Serum Was Used, *Arch Dermat & Syph* **41** 265 (Feb) 1940.

49 Ebert, M. H., and Otsuka, M. Treatment of Pityriasis Rosea by the Injection of Typhoid Vaccine, *J A M A* **123** 1036 (Dec 18) 1943.

A Ninety patients were treated with a 1 500 dilution of trichophyton extract⁵⁰ All patients were tested for their sensitivity with 0.05 cc of this extract intradermally, isotonic sodium chloride solution U S P being used as a control Of the 90 patients, 95 per cent proved nonsensitive to this dilution Treatment was started forty-eight hours later Four to six intradermal injections of the same dilution were given three times a week in increasing doses (0.1, 0.15, 0.2, 0.25, 0.3 and 0.35 cc) over a period of two weeks

Itching, whenever present, stopped after the second or third injection The eruption disappeared entirely or was only faintly visible after three to six injections Four patients did not improve The result of this experiment was published in 1945 in the form of a preliminary report⁵¹

B In this group 60 patients were treated with a 1 500 dilution of Lederle's oidiomycin (a broth culture product of "Candida albicans") Again all patients were tested for their sensitivity with 0.05 cc of this extract intradermally, isotonic sodium chloride solution U S P being used as a control In contrast to the previous group treated with trichophyton extract, 90 per cent of these patients gave a positive reaction to "oidiomycin" Treatment was started forty-eight hours later One tenth of a cubic centimeter was given intradermally twice a week, the dose was not increased The results were slightly superior to those obtained in the previous group, treated with the trichophyton extract The lesions began to involute or disappeared completely after the second or third injection Pruritus, when present, ceased after one to two injections Results were the same whether the eruption had been of a few days or of several (two to twelve) weeks' duration In no case were ill effects noted from treatment Two patients did not respond

Group 2—Since the good results with both the "trichophyton" and "oidiomycin" extracts might have been due to a nonspecific factor, a group of 30 patients were treated with staphylococcus toxoid (digest modified)⁵⁰ All patients were tested for their sensitivity with 0.05 cc of this extract Ninety-five per cent of them reacted positively Treatment was started forty-eight hours later All the patients were given 0.1 cc of staphylococcus toxoid (digest modified) intradermally twice a week The results were similar to those obtained with "oidiomycin" Pruritus was no longer present after one or two injections, and the eruption cleared up within seven to ten days One patient showed no improvement

Group 3—This group consisted of 30 patients who received injections of a sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc)

A Fifteen patients were given 0.1 cc of this substance intradermally at two day intervals When tested for their sensitivity, only 2 of them reacted positively Four to six injections produced no change in the course of pityriasis rosea

B Fifteen patients received the same agent by intramuscular route Amounts of 5 to 10 cc were given in increasing doses twice a week, three to four injections in all Each injection was followed by a rise of temperature (101-104 F) within twenty-four hours Pruritus ceased after the third injection The eruption itself disappeared or became only faintly visible within twelve to fifteen days Two patients showed no improvement

Group 4—Finally simultaneously with each of the aforementioned groups of patients, those treated with trichophyton extract, "oidiomycin," staphylococcus toxoid (digest modified) and a sterile solution of lactalbumin in colloidal form, respectively,

⁵⁰ A product of Lederle Laboratories, Inc

⁵¹ Vass I Treatment of Pityriasis Rosea with Trichophyton Extract A Preliminary Report Arch Dermat & Syph 51 203 (March) 1945

15 patients with pityriasis rosea (60 in all) were given 0.1 cc of isotonic sodium chloride solution U S P intradermally for control. In these patients the disease took its usual course. It lasted from three to eighteen weeks. Pruritus, whenever present, remained unchanged.

All patients were advised to avoid soap and to stop wearing tight garments for the duration of treatment, as the lesions tended to persist at sites of friction and pressure. When pruritus was present, an antipruritic emulsion was prescribed for topical use.

The therapeutic ineffectiveness of injections of isotonic sodium chloride solution in the control group suggests that the basis of improvement was not psychologic.

All patients underwent a thorough examination for pathogenic fungi. None could be found in the lesions of pityriasis rosea, either on direct examination or by culture. Improvement was most rapid in those patients who showed a pronounced allergic response when tested for their sensitivity to the substances used.

Review of my material on 270 patients treated with "trichophyton extract" of "oidiomycin," staphylococcus toxoid (digest modified) and a sterile solution of lactalbumin in colloidal form, respectively, leads me to conclude that, on the whole, the results obtained by their use in the treatment of pityriasis rosea are not due to any specific action.

SUMMARY

Two hundred and seventy patients were treated for pityriasis rosea in four groups. Group 1 *A* received 0.1 cc of a highly diluted trichophyton extract intradermally in increasing doses three times a week, four to six injections being given in all. Group 1 *B* was given 0.1 cc of a highly diluted "oidiomycin" (a broth culture product of *Candida albicans*) intradermally in equal doses twice a week, three to four injections in all. Group 2 received 0.1 cc staphylococcus toxoid (digest modified) intradermally in equal doses twice a week, three to four injections being given in all. Group 3 *A* received 0.1 cc of a sterile solution of lactalbumin in colloidal form, injected intradermally in equal doses at two day intervals. Four to six injections were given in all. Group 3 *B* received a sterile solution of lactalbumin in colloidal form by intramuscular route. Amounts of 5 to 10 cc were given twice a week, two to four injections in all. Sixty patients, acting as controls, simultaneously with the patients in the aforementioned groups received intradermal injections of isotonic sodium chloride solution, U S P, 0.1 cc twice a week for a total of four to six injections.

In all but 8 patients treated with trichophyton extract, "oidiomycin" and staphylococcus toxoid (digest modified), respectively (group 1 and group 2), pruritus ceased after the second or third injections. The eruption itself disappeared or became only faintly visible within seven to ten days.

Patients treated with a sterile solution of lactalbumin in colloidal form by intramuscular route responded somewhat more slowly. Pruritus ceased after the third injection. The eruption itself disappeared or became only faintly visible within twelve to fifteen days. Two patients

did not respond Lactalbumin solution by intradermal route had no effect on the source of pityriasis rosea

In contrast to the considerably shortened course of pityriasis rosea when the aforementioned substances were used, in the control groups given intradermal injections with isotonic sodium chloride or lactalbumin solution the condition took three to twenty weeks to clear up These observations would appear to exclude the psychologic element as an essential factor in the favorable therapeutic response

All patients who were treated with these extracts underwent a thorough examination for fungi No recognized pathogenic fungi could

Summary of Results of Treatment

	Number of Patients Treated	Material Injected, Dosage	Number of Injections Given	Period Within Which Pruritus Ceased and Eruption Cleared
Group 1A	90	Trichophyton extract (Lederle Laboratories, Inc), 0.1 cc of a 1:500 dilution, intradermally 3 times a week	46	7-10 days
Group 1B	60	"Oridiomycin" (Lederle Laboratories, Inc), 0.1 cc of a 1:500 dilution, intradermally twice a week	24	7-10 days
Group 2	30	Staphylococcus toxoid (digest modified) (Lederle Laboratories, Inc), 0.1 cc intradermally twice a week	24	7-10 days
Group 3A	15	Sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc), 0.1 cc intradermally 3 times a week	46	3-20 weeks
Group 3B	15	Sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc), 5.10 cc by intramuscular route twice a week	34	12-15 days
Group 4 (control)	60	Isotonic sodium chloride solution U.S.P., 0.1 cc intradermally twice a week	46	3-20 weeks

be found either on direct examination or by culture in the lesions of pityriasis rosea

CONCLUSIONS

Good results were obtained with intradermal injections of trichophyton extract and "oridiomycin," staphylococcus toxoid (digest modified) and intramuscular injections of a sterile solution of lactalbumin in colloidal form, respectively, in the treatment of pityriasis rosea No such results were obtained by intradermal injections of isotonic sodium chloride or lactalbumin solutions The theory is expressed that the results were probably due to a nonspecific effect of the active substances The investigative study of 270 patients did not show any evidence in favor of the fungous origin of pityriasis rosea

TRICHONODOSIS

Report of a Case

MARCUS A WEINER, M D

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A CASE of trichonodosis (knotted hair) was reported in 1947 by Pratt¹. To the present time that is the only report on this condition in the American literature. He quoted McCarthy² as stating that there are two types of trichonodosis: (1) a rare variety, occurring as solitary knots associated with abnormal hair growth, and (2) a commoner variety, occurring as single or multiple knots, resulting from mechanical forces.

Pratt's case was an example of the first variety. The following report deals with the "mechanical" type of trichonodosis, of which no account exists in the American literature.

REPORT OF A CASE

M S, a 46 year old white man, was seen at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on March 10, 1948. He complained of generalized itching and "parasites on the skin" of two years' duration. Past treatment elsewhere consisted of the application of various ointments and shaving of all hair (except on the scalp) on two occasions.

Examination revealed an excitable, intensely worried, intelligent man. On most of the body was a moderately dense covering of hair of rather fine structure, but curly. No cutaneous lesions were discovered. Pruritus was referred to in all cutaneous areas below the neck. Furthermore, the patient insisted that he could feel the "parasites" on his hair. He did, in fact, quickly locate a hair on the thigh which on close inspection revealed a barely visible body on the hair shaft. Microscopic examination disclosed a tight knot, as illustrated in the figure. There was no demonstrable disease either of the skin or of the hair.

Further examination of the patient disclosed dozens of knotted hairs on the trunk, thighs, buttocks, pubes and scrotum. The scalp hair showed no knotting. The patient stated that he had always had curly hair and was troubled frequently.

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1 Pratt, A G. Trichonodosis. Report of a Case, Arch Dermat & Syph 56: 267 (Aug) 1947.

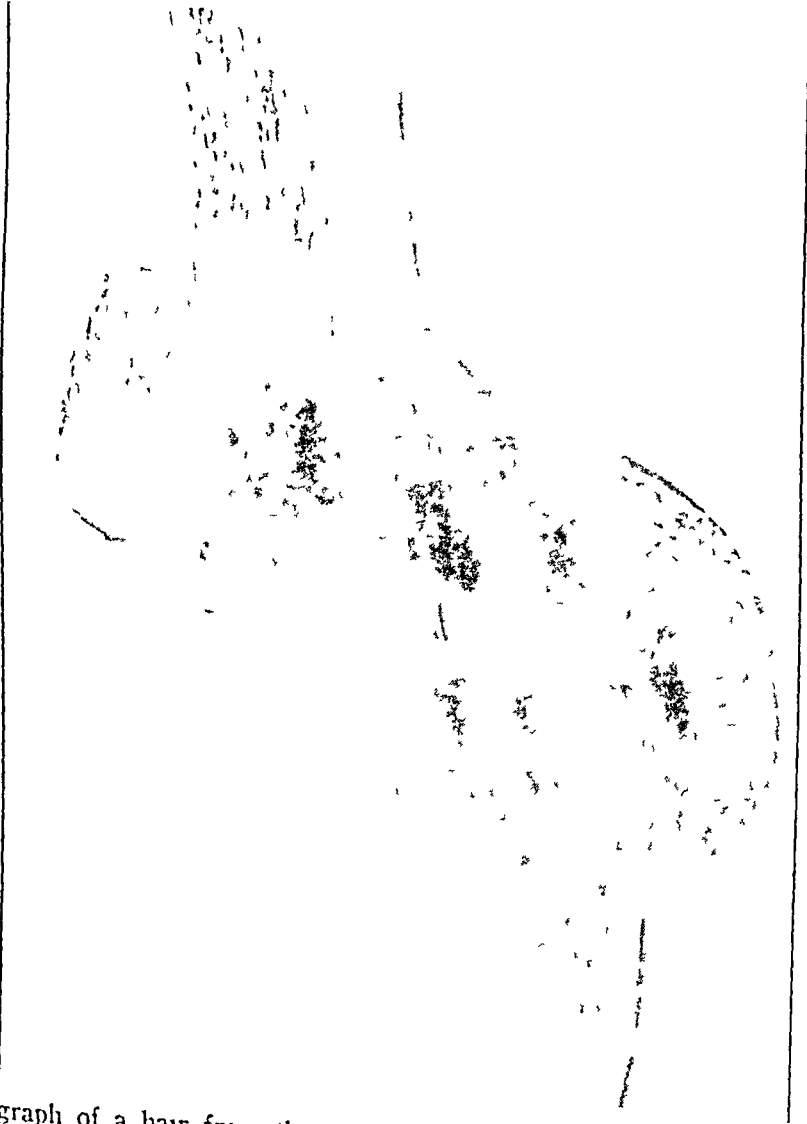
2 McCarthy, L. Diagnosis and Treatment of Diseases of the Hair, St Louis, C V Mosby Company, 1940, pp 103-104.

by "ingrown hairs" in the bearded region. He admitted that his pruritus developed after he became aware of the nodes on his hairs. He had been convinced for two years that he was infested with some type of "bug."

The diagnosis was trichonodosis and delusion of parasitosis (acarophobia).

COMMENT

It is not intended to convey the idea that trichonodosis is a rare condition. On the contrary, it is extremely common. I have on many occasions



Photograph of a hair from the patient reported, showing typical knotting

observed the presence of knotted hairs by chance while examining the skin closely. It seems to occur commonly in the pubic hairs. It causes no symptoms, and the patient is almost invariably unaware of its existence. After Galewsky³ originally described the condition, Kren⁴

³ Galewsky. Ueber eine noch nicht beschriebene Haarekrankung (Trichonodosis). Arch f Dermat u Syph 81 195, 1906
⁴ Kren, O. Ueber das Vorkommen der Trichonodosis (Galewsky), Wien. Wchnschr 20 916, 1907

found thirty-five instances of hair knotting in 54 women with various cutaneous diseases. In the only recent article on the subject (except that of Pratt¹) Cajkovac⁵ reported on 36 cases in which knotted hair was an incidental observation. He estimated that it occurs in about 10 per cent of patients with cutaneous diseases, particularly in pruriginous disease. He expressed the opinion that it was due to mechanical causes and was not dependent on skin changes or unequal hair growth.

I feel that, in cases of trichonodosis not associated with abnormal hair growth, curliness of the hair is an essential predisposing factor. Owing to the hair's curling, a loose knot is fortuitously formed. In patients, however, who scratch or rub the skin, who pull on the hairs or who constantly run their fingers through their hair, these loose knots are tightened to form a tiny node on the hair shaft, these nodes can then come into the patient's consciousness by virtue of their being felt or seen, as is exemplified in this case.

The paucity of reports dealing with this condition is undoubtedly due to its unimportance. However, it seems worthy of mention, if only to aid the recognition of the type of case herein described.

SUMMARY

A case of so-called mechanical type of trichonodosis (knotted hair) is reported. Its possible pathogenesis is briefly discussed. A severe degree of acarophobia was present in association with the hair knotting.

5 Cajkovac, S. Morphology and Pathogenesis of Trichonodosis, *Liječnič vjes* **61** 471, 1939.

PSORIASIS OF THE HYPOPHARYNX

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INVOLVEMENT of the mucous membrane in psoriasis is a most unusual feature of this disease. Though accepted by most leading authorities it has been seen only by a few. Usually it is the buccal mucosa (the cutaneous region of Jadassohn and Schuhmacher), the tongue, the palate and the lips that are involved.

Up to the time when Oppenheim first performed a biopsy in his case great confusion existed, since the terms leukoplakia and psoriasis buccalis (Bazin, 1868) were used synonymously. Since then, a goodly number of cases, with and without histologic examination, have been reported in publications or presented at dermatologic meetings.

Psoriasis of the conjunctiva and the vulva is even rarer than oral psoriasis, while involvement of the larynx is recorded in the literature only three times (Rugani, Paludetti). Rugani's patient had had psoriasis for many years. For the last three years that the condition existed, there was involvement of the larynx with each exacerbation of the cutaneous condition, as evidenced by pain and lowering of the voice. Laryngoscopic examination revealed small gray plaques on congested vocal cords. These lesions disappeared with the improvement of the cutaneous psoriasis. Rugani was able to see this phenomenon wax and wane five times in as many months. He quoted Paludetti as having seen 2 similar cases.

To our knowledge there is no case on record of psoriasis of the hypopharynx. Thus the following case was deemed worth reporting.

REPORT OF A CASE

A 60 year old man was admitted to The Mount Sinai Hospital because of progressive loss of vision. A craniotomy was performed, and a suprasellar meningioma was removed. The patient died three weeks later of massive pulmonary

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embolization The following statements in his history are of importance He had had psoriasis for forty-three years He neither smoked nor drank Reactions in repeated blood tests were negative for syphilis

Apart from the aforementioned observations and some incidental observations, the autopsy showed a characteristic scaly pearly white psoriatic lesion on an erythematous base on the extensor surface of the left forearm This area measured 12 cm in its longest diameter There was also a white fuzzy plaque 3 cm in



Fig 1—Psoriatic plaque in right side of the hypopharynx

diameter, surrounded by a red halo in the right pyriform recessus and on the adjacent wall of the hypopharynx (fig 1)

No definite diagnosis could be made from the gross appearance of the lesion The possibility of thrush had to be abandoned when smears and cultures failed to show *Monilia* organisms Sections were taken from the cutaneous and mucosal lesions for histologic study The former showed the characteristic appearance of an old psoriatic plaque, while the latter revealed a most unusual picture Firstly, there was a large degree of accumulation and desquamation of nucleated squamous epithelial cells analogous to the parakeratosis of cutaneous psoriasis (fig 2), accompanied with a focal disturbance of the stratified epithelium which in places

failed to show the normal prismatic basal cells. The prickly cell layer consisted of a few flattened cells in these areas.

Secondly, there was a conspicuous accumulation of amorphous eosinophilic material in the submucosa which appeared yellow in the Azan (Heidenhain) and van Gieson stains. This edematous infiltration contained collagen and elastin bundles that were widely spread apart (fig. 3). The normally scant papillae of this region were flattened out and obliterated by this edema. This accounted for the



Fig. 2—Pronounced piling up of nucleated squamous epithelium. The dark nuclei near the lower edge belong to epithelial cells (hematoxylin and eosin stain).
absence of acanthosis. The hyperemic ring of the lesion was explained by engorged submucosal vessels (fig. 4). (For a discussion of the halo of psoriatic lesions, see Herrmann and Kanof.)

COMMENT

Some of the authors describing psoriasis of the mucous membrane have performed biopsies of these lesions. However, their microscopic observations were not uniform and, in some instances, were even contradictory. Most of the writers described parakeratosis, hypertrophy

of the epithelium (acanthosis), intercellular and intracellular edema, cellular infiltration and edema of the submucosa (corium) in varying degrees

The unique localization of the lesion in our case accounts for the somewhat different histologic appearance. The submucosa of the hypopharynx and adjacent regions is unusually loose (as indicated by the



Fig 3—Edge of the lesion with almost normal epithelium. The submucosa is widened by edema which fades out to the right (Weigert-Van Gieson stain for elastin)

ease with which supraglottic edema develops in this site). The pathologist is familiar with the frequent agonal edema of these parts caused by the supine position of the body. It is this looseness of the submucosa which explains the exaggeration of the well known edema of psoriasis. This edema stretches the normally scant papillae of this region and flattens them out, and this makes quite comprehensible

the absence of the usual psoriatic acanthosis. The piling up of the epithelium and the large sheets of nucleated surface cells are analogous to what is seen in cutaneous psoriasis, as is the engorgement of the vessels. The fact that there was only a solitary psoriatic plaque on the skin does not militate against the diagnosis of psoriasis of the mucous membranes, since mucosal lesions may have a course independent of cutaneous exacerbations.



Fig 4—Engorged vessels arranged radially and parallel to the surface

Leukoplakia is ruled out principally by the absence of a stratum granulosum and a stratum corneum.

SUMMARY

The first case of psoriasis of the hypopharynx is described and the differences in the microscopic picture accounted for by the looseness of the submucosa in this region. Hypertrophy of the epithelium

with parakeratosis and an impressive degree of edema of the submucosa dominate the histologic picture

1 East One-Hundredth Street (29)
Atenas 3

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Book Reviews

Occupational Marks and Other Physical Signs A Guide to Personal Identification By Francesco Ronchese, M D Price, \$5 50 Pp 181, with 151 illustrations New York Grune & Stratton, Inc, 1948

This is an interesting book, which the author created as a result of his hobby of examining patients for evidence of occupational marks. He has surveyed workers in most of the industries and trades and in various professions and has recorded, with photographs and drawings, the marks on the skin acquired from their work. The possibility of using such marks for identification of the dead, as well as their value to criminal investigators, is stressed.

The illustrations are numerous and good. The book is recommended to physicians in general, but especially to dermatologists and to those whose knowledge of occupational marks should be essential in their work.

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TEXTILE DERMATITIS IN MEN

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BEFORE commencing my subject, I should like to state how much I appreciate the honor of being asked to address the dermatologic section of the American Medical Association, and to express my warmest thanks to the President and the office bearers not only for their kindness in asking me, but for the generous reception which has been granted me. The Greeks, as usual, had a word for it "It is not given to every man to go to Athens" but I, a citizen of Edinburgh, sometimes called the modern Athens, believe that the United States is the lodestar of every medical man who wishes to advance his knowledge at the feet of brilliant doctors and at the most efficient clinics.

By textile dermatitis I mean dermatitis caused by textiles, whether dyed or undyed, I have excluded other articles of wearing apparel, such as shoes, hatbands and nickel accessories. It is not from any discourtesy that I have excluded the gentler sex from my discourse but for the excellent reasons that their wearing apparel is now so very complex and that contact dermatitis in women, to a greater degree than in men, is often bound up with hormonal and nervous influences. To quote the words of Cox¹

It has been well said that the modern Miss is the patron saint of chemistry, she is adorned from head to foot by the art of the chemist, and it must be agreed that if she avoids excesses she does look very attractive. The manufacturer aids and abets her in applying to herself all kinds of new compounds the nature and properties of which from our present point of view are little understood. Her hair, having been bleached with peroxide and ammonia and shampooed with a soap substitute, is dyed with a compound diamine. Her eyelashes may be the product of the grease pencil, her lips and cheeks may derive their beauty not from oxy-haemoglobin but from eosin and ponceau, her teeth—natural or artificial—are brushed with a waterproof synthetic fibre, her fingers are adorned with nitro-cellulose dissolved in complex solvents and plasticized with still more complex chemicals. Perhaps she has applied chloramine T or an oxyquinoline derivative to her axillae or even used mercaptoglycolic acid as a depilatory. But I want to

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Meeting of the American Medical Association, Chicago, June 23, 1948

¹ Cox H E. Chemicals in Fabrics as Potential Skin Irritants, Brit J Dermat 54:22 1942

pass from these personal details to consider more particularly what she is wearing. Perhaps she has a corset made of latex rubber with fillers and antioxidants in it, a bleached woollen vest impregnated with synthetic finishes, other intimate garments made of cotton with synthetic resins as anti-crease, stockings of de-lustred viscose, a frock of rayon containing perhaps regenerated cellulose and cellulose ethers impregnated with quaternary ammonium compounds to render them water-resisting, her shoes are made of new plastics resembling snake skin, and her fur cape is of leopard skin in which the familiar spots have been produced by mating a polyphenol with a diamine. Possibly she has spectacles of synthetic glass with sides of plastic resin, a handbag of suede leather compounded of cotton and rubber and an orchid made from doped or dyed cellulose in her buttonhole, perfumed with otto of the laboratory, not attar of rose. She is in fact one grand experiment, small wonder that Nature sometimes revolts. A rash appears, she goes to the doctor.

You will thus see that I have plenty of excuse for excluding the female of the species and selecting a topic which is not nearly so difficult. I have selected it for several reasons, the first being that the conditions which I am about to describe had not been diagnosed by general practitioners, not infrequently this type of dermatosis is not recognized even by dermatologists. Secondly, these eruptions if untreated tend to develop into circumscribed neurodermatitis and may be extremely difficult to cure, so early recognition and treatment are important. Thirdly, I wish to learn whether such cases are encountered in the United States, as I can find few references in the literature of this country.

My task has been made easier by several factors. Certain types of contact dermatitis due to clothing no longer exist. As Cox¹ said,

‘ Most of the known deleterious dyes have gone out of use. Very fast insoluble dyes are now available, and standardized tests for fastness and absence of bleeding have been described by the Society of Dyers and Colorists. ’ Nowadays one never sees dermatitides due to resin finishes in underwear, such as were described by various authors in the United States between 1941 and 1943². The Spartan simplicity of life in Britain today, with the difficulty of buying new garments, renders my problem much simpler. One might therefore conclude that my paper ought to be as brief as the famous chapter on snakes in Horrebow’s book on Iceland. This chapter contained only six words: “There are no snakes in Iceland.”

² Cannon, A. B. Contact Dermatitis (Underwear Shorts), *Arch Dermat & Syph* **44** 1157 (Dec.) 1941. Neilson, A. W., and Reches, A. J. Contact Dermatitis Due to Underwear. Observations in Fourteen Cases with Summary of Efforts to Discover the Cause, *ibid* **44** 218 (Aug.) 1941. Schwartz, L. Dermatitis from New Synthetic Resin Fabric Finishes, *J Invest Dermat* **4** 459, 1941. Gould, A., Beresford, H., and Moore, N. Resin Dermatitis from New Pajamas and New Shorts, *New York State J Med* **41** 2236 1941.

HISTORICAL SURVEY

It is only within recent years that attention has been drawn to textile dermatitis, though Killick and Ingram³ quoted the description given by White, in 1897, of 5 cases of dermatitis following the wearing of unwashed black cotton shirts dyed with aniline black and noted that this condition is probably commoner than the lack of information would suggest.

After 1897, there is little evidence that such conditions were recognized until the appearance of the article by Killick and Ingram, though attention had been drawn to fur dermatitis. Simon and Rackemann⁴ described a single case of a man with a chronic relapsing eczema due to garments containing a variety of dyes, especially the azo group, and Bonnevie and Genner,⁵ in noting 15 cases of eczema due to dyed clothing, observed that all but 1 were in women. They noted that the localization of the eczema was often distinctive, the eruption appearing in the axillas, in the bend of the arms and on the neck, and that the areas were those where contact with the clothing was most intense.

There appears to be no reference in the literature to dermatitis due to khaki clothing during the war of 1914 to 1918, though Low⁶ saw not a few patients with such conditions, all of which were of a mild type and appeared to be more in the nature of traumatic dermatitides than of true eczematous reactions.

In the recent World War, however, dermatoses due to khaki clothing were by no means uncommon. In the years 1944 and 1945, in Italy, I saw not less than 67 instances. In a stimulating paper, Davies and Barker⁷ reported a variety of cutaneous manifestations due to various textiles, such as army clothing and blankets. These took many forms, such as pruritus, erythema, erythematous dermatitis, eczematoid dermatitis, facial eczema, prurigo simplex, urticaria, acneiform and pustular rashes and prurigo simulating scabies. Of 201 cases, few were like those about to be described, which resemble more closely those noted in persons on military service in hot climates, in whom

³ Killick E. M., and Ingram, J. Dermatitis Following the Wearing of Dyed Fabrics. *Lancet* **1** 77, 1933.

⁴ Simon, F. A., and Rackemann, F. M. Contact Eczema Due to Clothing, *J. A. M. A.* **102** 127 (Jan 13) 1934.

⁵ Bonnevie P. and Genner, V. Fifteen Cases of Eczema Due to Dyed Clothing in *Forhandlinger ved Nordisk Dermatologisk Forening*, Copenhagen, 1926, p. 457.

⁶ Low R. C. Personal communication to the author.

⁷ Davies I. H. T. and Barker, A. N. Textile Dermatitis, *Brit J. Dermat* **56** 11 1944.

a more acute type of eruption tends to develop, partly because of the hyperhidrosis induced by a hot climate and partly because khaki drill clothing was worn in these areas

In 1944, Carpenter and Banzer⁸ described 3 cases of dermatitis due to the wearing of blue naval uniforms, the lesions appearing chiefly on the upper and inner aspect of the thighs and the inner aspect of the arms and on the cubital fossae and wrists. Such eruptions were occasionally seen in British naval personnel. In the series of cases about to be described, 1 man volunteered that his rash, which was caused by a blue suit, had first started when he was in the Navy.

In 1946, Howell⁹ analyzed the causes of contact dermatitis in 250 patients seen within a year and noted that 2 patients were affected with eczematous outbreaks due to khaki clothing. He stated that 1 patient had a pruritic, eczematous eruption on the greater portion of the entire body, the face and hands were unaffected. Thickened weeping areas were noted over the base of the neck posteriorly, in the axillas and popliteal regions and along the waist line. After approximately two or three months' observation, the possibility of khaki clothing as a cause of the dermatitis was considered. A forty-eight hour patch test elicited a questionable positive reaction, the rash quickly improved after the patient's admission to hospital, only to recur when he again wore a khaki shirt.

CAUSE OF ERUPTIONS

During the two years preceding this report, I have been impressed by the number of cases of textile dermatitis occurring in men. The total number of new outpatients in the department of dermatology of the Royal Infirmary, Edinburgh, during the two year period was 12,680, of these, 64 men had textile dermatitis. (As a comparison, the number of cases of lichen planus was 77.) In 6 of the 64 cases, the dermatitis was due to blue garments, in 1 to red wool and in 5 to undyed wool. In all the other 52 cases the eruption was provoked by khaki material in 23, by drill shirts, in 18, by woolen shirts, in 3 by both drill and woolen shirts, in 5, by battle dress, and in 2, by jerseys worn next to the skin because of the shortage of underwear (Nowadays in Britain new clothing is not easy to procure, while surplus army shirts are cheap and unrationed, so men frequently wear them at work.)

8 Carpenter, C. C., and Banzer, J. W. Dermatitis from Blue Uniforms, *U S Nav M Bull* 43 754, 1944

9 Howell, J. B. Contact Dermatitis. An Analysis or Tabulation of All Cases Proved in a Single Year, *Arch Dermat & Syph* 53 265 (March) 1946

TYPE OF ERUPTIONS

With a little practice one soon became proficient at diagnosing the type of garment responsible for the particular rash. The khaki drill shirt, somewhat hard in texture, in the early stages produced an erythematopapular rash, characteristically on the cubital fossae, the axillary folds (but not in the apex of the axillas), and the sides of the neck, though sometimes there was also a papular rash around the waist, over the sacral region, on the penis and on the thighs and buttocks. If the shirt was worn for several months, the papular rash became a weeping, crusted dermatitis and finally became indistinguishable from a plaque of circumscribed neurodermatitis associated with intense pruritus (fig 1).

When the dermatitis was caused by khaki-colored woolen shirts the bend of the arms, the axillary folds and the sides of the neck,

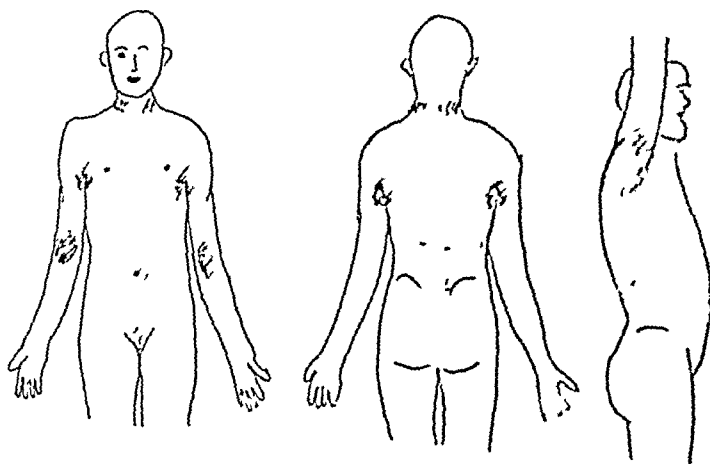


Fig 1—Distribution of eruption in dermatitis due to the wearing of khaki drill shirts

were involved, but there was also an extensive eruption over the deltoid, scapular and interscapular regions, extending over the buttocks. Often an area of healthy skin extended across the lower part of the back on a line between the iliac crests. Dermatitis due to woolen shirts rarely developed into circumscribed neurodermatitis. These patients often had greasy, seborrheic skins.

Khaki woolen jerseys provoked a picture essentially similar to that caused by the woolen shirts, while the dermatitis due to battle dress caused a typical distribution, affecting the sides of the neck, the bend of the legs, the inner aspect of the thighs, and the wrists, calves, knees and often the buttocks.

The distribution of the rash due to undyed wool, seen in 5 cases varied according to the contact of the patient's skin with the garment or garments. Not only woolen underwear and shirts, but also woolen suits, socks and gloves, were sufficient to produce pronounced eczematous

reactions In a patient wearing a woolen vest the distribution resembled that of a severe rash due to a khaki woolen shirt

In 6 cases blue dyes were responsible for the eruption, the distribution of which depended on the garments worn, these were of various types, such as socks, singlets, suits, jerseys and linen shirts In a single instance a red wool jersey worn next to the skin caused



Fig 2—Purpuric contact dermatitis, possibly caused by an unknown substance used as a stiffener in new khaki woolen shirts

the rash, but it was impossible to determine whether it was due to the wool or the dye, which appeared to be fast

Perhaps the most interesting condition was purpuric textile dermatitis, 5 cases of which were recorded in the series (fig 2) During army service in Italy, I had the opportunity of seeing a number of examples,¹⁰ but Hodgson and Hellier,¹¹ in an excellent paper, described

10 Peterkin, G A G Purpuric Type of Textile Contact Dermatitis, Correspondence, *Brit M J* **1** 106, 1946

11 Hodgson, G A, and Hellier, F F Dermatitis Caused by Shirts in *B L A J Roy Army M Corps* **87** 110, 1946

the eruption fully on the basis of their experience with 391 patients, seen between September 1944 and September 1945 in France and Germany. The dermatosis consisted of shiny, nonfollicular papules on the forearms, arms, axillary folds, abdomen, trunk, upper parts of the thighs and dorsum of the penis, with pityriasis-rosea-like lesions and erythroderma on the back of the shoulders, on the sacral triangle and over the greater trochanter. The rash was interspersed with fine petechiae and with linear purpuric streaks. It was not a wool dermatitis, as only 28 per cent of patients were intolerant to wool, as compared with 31 per cent of 123 persons in a control group. Reaction to a patch test to unwashed khaki shirts was positive in 36 per cent. Response to a cuff test was positive only if the rash had previously affected that area. Large doses of ascorbic acid did not help to clear the eruption. Experience indicated that results of patch tests might be unreliable evidence, that they might vary in the same patient when a test was repeated, and, of course, that the tests do not reproduce specific circumstances which exist when an irritant is reaching the skin from the shirt. In conclusion, Hodgson and Hellier decided that the rash was due not to the wool, not to the dye nor to dichlorodiphenyltrichloroethane (DDT), with which the shirts were impregnated, but to some unknown substance, probably used as a stiffener.

Independently, I came to somewhat similar conclusions as all my patients with the disease had recently donned a new type of khaki woolen shirt made in the United States, and while patch tests to DDT, to a 3 per cent solution of potassium dichromate and to other khaki shirts gave negative reactions, tests with this type of shirt, with collar attached, frequently gave positive reactions. I considered that diet might well play a part in the causation, as all the patients were seen during the winter months, the 5 in the present series in the months from January to April. Though the exhibition of ascorbic acid did not aid recovery, it seemed to me that rose hip syrup and black currant juice speeded the cure, so lack of vitamin P may have been involved. However, many of Hodgson's and Hellier's patients had been eating plenty of fresh fruit just prior to the appearance of the rash.

Of the 5 patients seen in 1946-1947, the rashes of 4 were due to the woolen khaki shirts, but that of 1 patient was caused by a woolen khaki jersey worn next to the skin, a similar dermatosis appeared in a young girl as the result of wearing a brown wool bathing suit, the eruption being limited exactly to those areas of skin covered by it.

REPORT OF CASES

CASE 1—G P, an insurance apprentice aged 17, bought a khaki drill shirt from an army surplus store and put it on for the first time on a Friday evening after work. He again wore the shirt on Saturday afternoon and on Sunday. On Sunday evening, an erythematopapular rash, extremely pruritic, appeared on the sides of the neck, on the axillary folds, the bend of the arms and the sacral triangle and in the small of the back. On Monday he visited the infirmary for advice and was informed that the rash was due to the shirt. A patch test of the material was applied to the unaffected skin of the forearm, and a positive reaction, in the form of an erythematopapular rash, appeared in twenty-four hours. The patient was given a bland paste consisting of 1 per cent ichthammol (ichthyol®) in zinc oxide ointment, on application of this the eruption disappeared within seven days.

CASE 2—J H, aged 42, a shepherd, for over two years had had a dermatitis which healed and relapsed for no apparent cause, his doctor had treated it with many local applications, without success. It had first appeared as a red, spotty rash around the neck, on the axillary folds, the cubital fossae and around the waist. It became much worse if he sweated profusely or was soaked in the rain. Gradually the affected areas became raw, with pronounced exudation, and eventually they evolved into thick, toughened patches which were intensely itchy. Inquiry revealed that he was the possessor of two woolen khaki shirts, which he wore frequently but often discarded in hot weather, when the dermatitis healed. Examination showed typical plaques of circumscribed neurodermatitis on the sides of the neck, the axillary folds and the bend of the arms, with a papular rash around the umbilicus and in the hollow of the back. He was instructed to stop wearing the shirts, and the lichenified patches were treated with a single dose of roentgen rays (250 r) and application of coal tar. The patient made an uneventful recovery.

CASE 3—J McK, a soldier aged 21, was issued a new shirt made of khaki wool, with collar attached, in February 1948. A fortnight later he noticed a rash affecting his arms, axillary folds, waist, sacral area and buttocks. He reported for examination by his medical officer, who referred the man to a venereal disease clinic, as the eruption was not itchy and had some resemblance to syphilitic roseola. When seen by a dermatologist, the rash was diagnosed as a typical example of purpuric textile dermatitis, with the characteristic small purpuric spots, linear hemorrhages and mild erythemosquamous patches. The only treatment advised was that he should discard this type of shirt and that he should be given large quantities of rose hip syrup. His case, however, could not be followed up.

PATCH TESTS

Provided one realized the limitations of the patch test, the procedure was frequently useful in the confirmation of diagnoses in these cases. In the cases of dermatitis due to undyed wool a positive reaction was invariable. The same applied to the cases in which the eruption was caused by blue garments, the patient's skin reacting to a small portion of the material dampened with water. The blue dye usually "bled" easily, so that it could be readily extracted from the cloth in warm water.

With khaki textiles, however, a positive reaction was by no means always obtained, it was oftener obtained, however, if the piece of cloth to be applied was soaked first in the sweat of the patient's

axilla. On the other hand, all patients who reacted positively also had a pronounced positive reaction to a 3 per cent solution of potassium dichromate (fig 3). The most practical proof that the garment was the cause of the rash was to have the patient cease wearing the suspected garment for a fortnight and resume the wearing of it at the end of that period, thus causing a typical exacerbation. This method was described by Davies and Barker⁷ as the khaki tolerance test or "K T T."

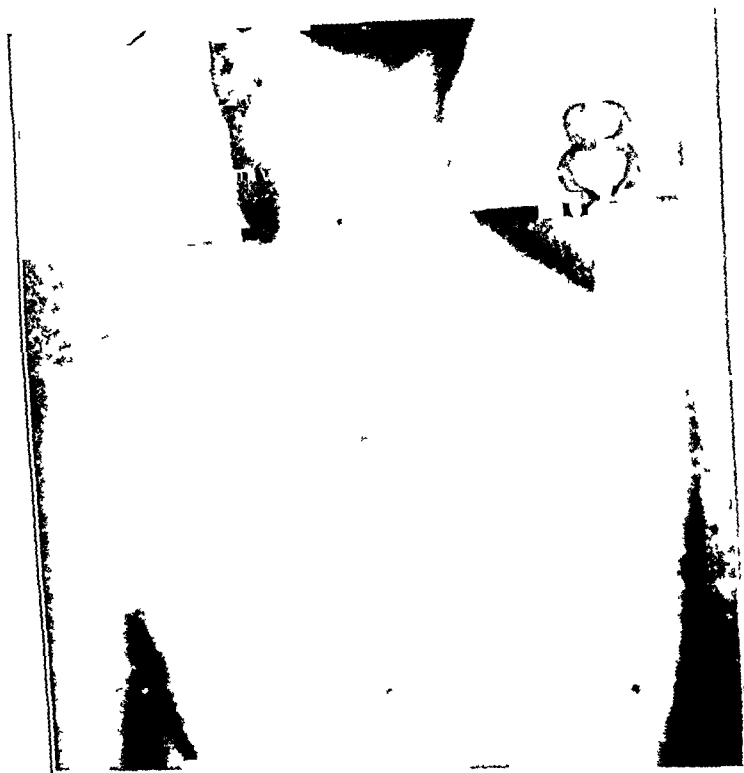


Fig 3—Reaction to patch test with 3 per cent solution of potassium dichromate.

ETIOLOGIC FACTORS

Why should 64 men have acquired a rash on wearing these garments, when so many others could wear similar ones with impunity? Several factors played a part, but the main one was the material of which the garment was made, especially the dichromate used as a mordant in the dyeing process. In a masterly paper on dermatitis from wearing apparel, Schwartz and Peck¹² stated "In mordant dyeing the excess of the oxidizing or mordanting bichromate should be removed. Of the mordants it is the dichromates which have caused dermatitis." This, then, is the main cause of the eczematous eruption in the patients wearing khaki clothing. Several of them

¹² Schwartz, L., and Peck, S. M. Dermatitis from Wearing Apparel, *J A M A* **128**: 1209 (Aug 25) 1945.

gave a previous history of sensitivity to chromium, e g, 1 had a rash on his wrist whenever he wore a chromium-plated watch, while 2 others had had dermatitis of the dorsa of the feet due to the chromate in the tongues of boots

In the 6 cases of eruption provoked by blue garments it was not possible to discover the type of dye used, but the color "bled" easily and patch tests were invariably positive As Bonnevie and Genner⁵ so truly stated, "This chemical aspect of the matter is indeed rather difficult to clear up, however, as the manufacturers are not willing to furnish information about this particular point" In the 5 men who had dermatitis due to undyed wool any woollen garment tended to produce dermatitis, for instance gray woollen socks a woollen scarf or a blanket, as well as underwear would cause an eczema on the site of contact, and the reactions to patch tests were positive

Though Lord¹³ noted, in describing 4 cases (2 of urticaria and 2 of eczema), that "cutaneous eruptions definitely due to sensitivity to wool have been but rarely encountered in dermatological practice," it is my opinion that such sensitivity is far from uncommon, but that most people soon realize that they cannot tolerate woollen material near their skin and so avoid it and the consequent dermatosis

Previous Dermatologic Conditions—In not a single patient of this series was there any family history of eczema, asthma or hay fever, nor did any of them give a history compatible with atopic eczema, the distribution of the eruption, however, was not unlike that of this form of eczema and occasionally caused this diagnosis to be made Eighteen patients of the group had once had dermatologic conditions 2 infectious eczematoid dermatitis of the legs, 2 circumscribed neurodermatitis, 3, dermatitis due to lime or cement, 2 tinea corporis, 2, eruptions due to drugs (arsenic, 1, phenobarbital, 1), 3 scabies, and 4, dermatitis due to benzyl benzoate given in treatment of scabies

Accompanying Factors—Pityriasis Simplex Capitis Bonnevie and Genner⁵ observed in their cases of textile dermatitis that pityriasis simplex, obesity and hyperhidrosis were frequent concomitants In the present series, over 60 per cent of patients had profuse dandruff and in several there were the oval, greasy, petaloid lesions of seborrhea corporis on the sternal or interscapular areas

Type of Persons Involved—few of the men were actually obese, but almost all were well covered with oily, sweaty skins They were generally full blooded, with a hearty appetite for fluids such as beer and tea

Hyperhidrosis Hyperhidrosis was almost always in evidence, not being localized to the axillas, palms and soles. It was certainly not due to emotional tension, as the men involved were frequently of the stolid, bovine type.

Age The factor of age did not seem to be important. The eruption occurred in men ranging in age from 17 to 71 but most were between 30 and 50 years of age.

Occupation This factor, likewise, was unimportant as cases occurred in all sections of the population, though miners were most frequently affected.

Distribution of the Eruption The rash was localized by two factors: the friction of the material on the skin, so that the sides of the neck, the axillary folds and the cubital fossae were the typical sites; and the perspiration, which tended to liberate the dye or mordant and also favored an eczematous reaction. In this connection, it may be interesting to quote what Burtenshaw¹⁴ stated regarding the secretions of the skin:

Mosher found that eccrine sweat, collected from well-washed skin on rubber sheets, varied in reaction between pH 5.42 and 5.91. If apocrine sweat was not excluded then the pH might rise to 8.4. Whitehouse, employing the British Drug Houses "capillator" method, determined the pH of sweat obtained from the washed back and leg as 4.6 to 5.0 but that of the face and armpit sweat as 7.0. Marchionni and his colleagues delineated more exactly the gaps in the acid mantle of the skin. To the more alkaline areas already mentioned they now add the '*vordere und hintere Schweissrinnen*,' namely the strips of skin stretching from the manubrium sterni to pubis and from the spines of the lower cervical vertebrae to the gluteal cleft. The skin of the flexures, where evaporation is slow and decomposition favored, also possesses a less than average acidity.

These factors apply exactly to the distribution of the rash in dermatitis due to a shirt.

Duration of the Disease Duration varied considerably, some patients being referred for advice within two days after the appearance of the rash, while others had had it as long as nine or ten years before it was diagnosed; the latter were the men who had large raw, weeping areas or patches of neurodermatitis. As a rule the patient's condition was diagnosed and treated effectively only after it had been present for several months. In the 37 men able to give a reasonable estimate the disease had been present for an average period of twenty-one and a half months.

TREATMENT

In the average case of contact dermatitis, it is sufficient to withdraw the external irritant and so permit the skin to heal spontaneously. This, of course, is what happens with the majority of patients with

¹⁴ Burtenshaw, J. M. L., in MacKenna, R. M. B. *Modern Trends in Dermatology*, London, Butterworth & Co., Ltd., 1947, p. 165.

textile dermatitis, and no treatment is required once the man ceases to wear the garment. In those cases in which the condition has persisted for months or years, however, the position is very different, and thorough treatment is needed to obtain a cure. In many the skin has become eczematized and secondarily infected, and in others the eruption has been transformed into a circumscribed neurodermatitis.

Thus the local applications one employs must be carefully selected. It is important to recognize that the skin of these men seldom, if ever, will tolerate greasy applications, so that ointments, water-miscible creams and thin pastes are contraindicated. In the milder cases a suitable application is a 2 per cent solution of ichthammol in calamine lotion two or three times daily, and in cases of the exudative form a suitable one is a 1 per cent solution of silver nitrate in spirit of ethyl nitrite, similarly used. When the skin becomes dry and scaly or if a circumscribed neurodermatitis has supervened, the dermatosis responds best to coal tar, painted on as a varnish twice a week and dried by dusting with talc, or to roentgen therapy, which is more effective in doses of 250 to 300 r than in fractional doses.

Undoubtedly, some patients with chronic cases are helped toward recovery if they adopt the dietetic regimen recommended by Barber¹⁵ for "seborrhic" eruptions—restriction of fluids with a high protein diet—though the latter is somewhat difficult to achieve in postwar days. Most of the patients had a high fluid intake as they were prone to imbibe large quantities of tea and beer.

COMMENT

One so often encounters in women cases of contact dermatitis due to garments that it seems worth reporting these 64 cases of dermatitis due to male garments, such as shirts, jerseys, underwear and trousers, noted in one city within two years. It should be realized, however, that 52 of them were produced by woolen or drill material which had been dyed khaki in color, and that the rash was chiefly caused by the dichromate used as a mordant. It would thus seem that the cases were a natural sequel to a war and that once world conditions return to normal the dermatosis may no longer be seen. On the other hand 4 of the patients had had the dermatitis for over nine years, having bought their khaki shirts before the outbreak of war.

Sensitivity to nickel is so well known that most cases are readily recognized, but it is possible that many cases of sensitivity to chromium occur and are not suspected. Schwartz and Peck¹² stated "Dermatitis from wearing apparel is not difficult to diagnose. The eruption begins at the place of contact with the offending material, usually five days or

15 Barber, H. W. Importance of Diet and General Treatment in Dermatology Practitioner **142** 1, 1939

more after the garment has been worn." However, in the present cases large areas of skin in contact with the clothing were unaffected, as the sites of the rash were determined by the friction of the garments and by perspiration. It was significant also that the condition was not recognized immediately, by any means.

In cases of industrial dermatitis the role of chromium is well known, but now and again chromium or its salts are incriminated as the cause of a less obvious eczematous outbreak. A good instance of this is given in the paper by Rabeau and Ukrainczyk,¹⁶ who showed that many cases of dermatitis in laundry workers were due to "eau de Javel," which is a solution of sodium hypochlorite to which potassium dichromate had been added as a stabilizer. Tests revealed that the dermatitis was due to intolerance to both chromium and chlorine, it appeared that sensitization of the skin to chromium had preceded and paved the way for the reaction to chlorine.

Undoubtedly, it would seem wise to bear in mind the possibility of a dermatitis due to clothing in any patient with a rash affecting all or any of the characteristic locations (sides of the neck, axillary folds, cubital fossae and waist, particularly over the sacral triangle). The remarks of Ingram¹⁷ are pertinent.

Localisation of value and importance here is that of the axillary eruption which leaves the dome of the axilla clear, since contact occurs only below the axilla and round the axillary folds, whereas seborrhoeic dermatoses show their maximum affection at the axillary apex. When eruptions are provoked by dyed socks, hat-bands, wristlets &c, the limitations are usually suggestive. In the case of dermatitis from dyed shirts localisation may be less precise if that garment is worn next the skin, but the axillary eruption often gives the clue. It is usual for a patient suffering from dye dermatitis to recover readily when the cause is removed, but it must be recognized that the reaction may, for constitutional reasons, persist for months or years. Under such circumstances it is usually probable that if the dye had not done so, some other hazard would have provoked the constitutional breakdown or manifestations other than dermatological would have arisen.

Ingram also noted that, though a tentative diagnosis of dye dermatitis is commonly made, subsequent investigation and observation show that dye dermatitis of any type is rare. In a series of 8,000 outpatients seen at his clinic he noted only 16 cases of dermatitis due to dyestuffs. Of these 16 cases, 6 were attributable to hair dyes, 3 to fur dyes and 7 to fabric dyes, including 2 cases from the wearing of khaki shirts.

Despite the supposition that cutaneous reactions to wool are rare, Davies and Barker⁷ stated the belief that all the types of eruption in their series of 201 cases were mainly referable to intolerance of the

¹⁶ Rabeau, H, and Ukrainczyk, F. Dermates des "blanchisseuses," rôle du chrome et du chlore (en France), *Ann de dermat et syph* 10 656, 1939

¹⁷ Ingram, J. Dermatitis from Dyed Hair, Furs and Fabrics, *Lancet* 2 239, 1935

skin to wool. Some of the reactions to the patch tests they applied were so severe as to produce ulceration, with consequent scarring. Their patients were all service men, many of whom had not been accustomed to wearing rough woolen material next their skin. Certainly, there are an extraordinary number of people with apparently healthy skins who, either in summer or in winter, will not or cannot tolerate woolly underwear or shirts. No doubt these folk, if forced by circumstances to apparel themselves thus, would in due course acquire a dermatosis. It was noticeable that during the cold weather in Britain, when there was a great shortage of fuel, men naturally wore warmer underwear and shirts. This may have accounted for the 5 cases due to woollens.

SUMMARY

The comparative rarity of dermatitis due to men's garments is commented on and contrasted with the vast scope for the occurrence of such dermatitis among women. Sixty-four cases of dermatitis due to men's clothing, seen within the past two years, are described and the etiologic factors noted. In 52 cases the dermatitis was provoked by khaki garments of various kinds, the rash in 5 of these cases was purpuric. Undyed wool was responsible in 5 cases. In a single case a red woolen jersey was responsible, though it could not be determined whether the cause was the red dye, the wool or an unknown factor. In 6 men the dermatitis was due to blue clothing, of various types, such as socks, singlets, linen shirts, suits, or jerseys in 1 case, worn next to the skin.

The importance of early diagnosis is stressed, as some of the patients had been affected for several years, and the average duration of the ailment in those able to give an accurate statement was twenty-one and a half months, in several patients patches of circumscribed neurodermatitis had developed on the typical sites of the rash, while in others a chronic weeping eczema had become established.

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ABSTRACT OF DISCUSSION

DR JOHN GODWIN DOWNING, Boston. Peterkin's excellent treatise leaves little to add. The diagnosis of a dermatitis due to a textile or to a type of garment may be very difficult. The condition may simulate scabies, pityriasis rosea, purpura, nummular eczema or several other entities. The exact cause is often difficult to prove. Every substance that goes into a garment may be sensitizing to some one person. The substance may act individually, or through a combination of factors peculiar to the material or to the wearer.

Dr Peterkin proved that the dermatitis in 5 cases was due to undyed wool. I look constantly for cases of epidermal sensitization due to wool, but rarely find them. Very few cases exist, even in industry. American boys of previous generations hated itchy woolen underwear, patients with atopic conditions, in fact, those afflicted with any pruritic disease of the skin, cannot wear woolen clothing.

next the skin. The reason is not sensitization, but mechanical irritation, affecting especially the areas of greatest friction—namely, the wrists, the cubital areas, the axillary folds, the sides of the neck and the waistline. Spinning is the forming of threads by drawing out and twisting the fibers of the raw material. A microscopic view shows small barbs on the fibers of the wool. When the wool fibers are drawn out and twisted, these barbs hook together and give strength to the woollen thread. The coarseness of the material and the presence of these fine barbs produce the irritation.

In industrial workers fine follicular eruptions appear on the dorsa of the interdigital spaces and papular eruptions on the anterior axillary folds and the axillary lines of the upper portion of the chest. These are due to plugging of the orifices by the minute fibers. The papules are intensely pruritic, they frequently become septic. The workers are examined because of recurrent infections of the hands, usually accompanied with lymphangitis.

Dermatitis due to textiles causes great discomfort. Its recognition means cure of the patient. We owe Dr. Peterkin a debt of gratitude for his fine presentation of this subject.

DR. ELLWOOD C. WEISE, Bridgeport, Conn. Dr. Peterkin has presented a truly significant contribution. When I first heard the title of Dr. Peterkin's paper, I thought the subject might include dermatitides due to the many different and complex types of material which make up the wearing apparel of today, but his clarity of presentation soon made it evident that he was considering only the types of dermatitis due principally to dyed or undyed wool.

Dr. Peterkin's three reasons for selecting his subject contain much food for thought. One is in the form of a question, in which he asks whether such cases are encountered in the United States, as he can find few references in the literature. I can attest to this scarcity of reported cases, when I tried to read up on the subject I found the references few and far between, and most of them dated long ago. It seems that, as dermatologists, we have often been hesitant in labeling cases of dermatitis as definitely due to wool because we have been too busy in civilian practice to distinguish between the various factors involved, i. e., (1) the raw wool itself, whether acting as a sensitizing agent or as a mechanical irritant, (2) the undyed or unfinished wool (the so-called gray material), which, in reality, is already partially processed, (3) the dyed material and (4) those materials additionally processed with antirease, stiffening and water-resistant agents. The reporting of larger series of cases in a more detailed manner often requires an outbreak of epidemic proportions, such as that due to resin finishes in men's underwear which occurred between 1941 and 1943, or even a war, in which large segments of the population are compelled to wear apparel to which they have been unaccustomed.

Another reason for the absence of reports in the literature appears in Dr. Peterkin's paper itself. Of 12,680 outpatients with dermatologic conditions at the Royal Infirmary, only 64 men had textile dermatitis. This figure represents approximately 0.5 per cent of the total of those admissions. Of course, a breakdown of the 12,680 cases, including those in female patients, would make possible a more accurate picture of the over-all occurrence of this type of dermatitis in both sexes. However, of the 64 cases in men, the condition was provoked by khaki garments in 52, and undyed wool was responsible in only 5 cases. Therefore, true allergic sensitivity and mechanical, or friction, dermatitis due to undyed wool garments remain relatively rare. I wonder if these 12,680 cases included any of dermatoses in infants and young children, due to the woollen material of snow suits and other garments. If these cases were included, the incidence of this type of dermatitis would be boosted to some extent.

If wearers of wool garments are so seldom actually sensitized to them, what is the situation among employees in mills, who not only wear wool, but are continually exposed to it in various stages of manufacture? I visited two mills, close questioning revealed that in one mill only 1 or 2 cases of dermatitis per year had occurred among 1,460 employees, and that these had invariably arisen in the dyeing departments where chromates and alizarin were used. In the other mill, which dealt with undyed wool, the superintendent and medical director could recall only 2 or 3 cases resulting from the material in the past twenty-five years, during which period about 10,000 persons had been employed.

Granted that the observations of many authors regarding the comparative rarity of wool dermatitis are correct, the interest aroused by Dr Peterkin's paper will lead to the recognition of a greater number of cases in the future. Physicians generally, and even dermatologists, too frequently fail to recognize them. The general practitioner can be excused, but the dermatologist certainly should bear such a diagnosis in mind. Since hearing Dr Peterkin's description of the distribution and other characteristic clinical features of this condition, I must admit that there have probably been not a few patients in the diagnosis of whose conditions I have "missed the boat" in the past. Among the few cases I diagnosed correctly was that of a patient who wore light woollen undergarments and presented the characteristic distribution, the axillas themselves not being affected. The eruption consisted of small erythematous macular areas, many of which were of a pityriasis-rosea-like nature. Though the patient had a seborrhea of the scalp, the skin of the body was very dry. The latter factor has been present in several of my cases. A positive reaction to a patch test with material from the undergarments was obtained in seventy-two hours. A few treatments with roentgen radiation, and the substitution of cotton undergarments, cleared up the condition.

Dr Peterkin's second reason for selecting his subject, namely, that, if undiagnosed and incorrectly treated, this condition tends to develop into circumscribed neurodermatitis and to become extremely difficult to cure, presents a factor of common occurrence. In fact, even the eczematization and secondary infection are frequently more difficult to deal with than the primary condition. Therefore, early recognition is imperative.

DR G. A. GRANT PETERKIN, Edinburgh, Scotland. I was most interested in Dr Downing's statement, that this condition can simulate many different dermatoses, it certainly can. It is interesting to see how many of these cases first occurred after scabies or after treatment of scabies with benzyl benzoate. I did enjoy Dr Downing's remarks about the woollen industry, because in Scotland a fair amount of woollen goods, such as socks and underwear, are produced. I see patients referred by the insurance companies for compensation, and have been struck with the extreme rarity of these dermatoses.

Dr Weise gave me just the information that I wanted, the relative incidence of textile dermatitis in the United States of America. I had been wondering if the resin finish were still in use, or whether it had simply vanished like the snows of yesteryear. Dermatitis due to resin finishes does not appear in Britain at all.

With regard to the condition in infants and children, woollen garments play a definite etiologic part in certain dermatoses in children. That, however, is a subject in itself.

In the woollen mills, an extremely low incidence of dermatitis of all kinds has been noted in the border district of Scotland, at least in those mills with which I am familiar.

I must express my thanks to you all for the kindness of your reception.

HERPES ZOSTER OPHTHALMICUS

Results of Treatment with Transfusions of Convalescent Blood

F T BECKER, M D
DULUTH, MINN

HERPES zoster is a neuritis, probably infectious, which accounts for between 1 and 2 per cent of all cutaneous diseases.¹ Involvement of the ophthalmic division of the trigeminal nerve is one of the serious aspects of this infection, because the eye is affected in nearly 50 per cent of the patients, and one half of these have some loss of vision. By the use of convalescent blood in the treatment of herpes zoster ophthalmicus, Gunderson² was able to maintain good vision in 82 per cent of his patients.

It is my purpose to review briefly the present knowledge of this disease and to report an additional 5 cases of herpes zoster ophthalmicus that were successfully treated by injections of blood obtained from persons who had recovered from herpes zoster.

NEUROANATOMY

The ganglion of the trigeminal nerve, the gasserian, lies in the middle cranial fossa near the midportion of the pons. The principal function is sensory but the trigeminal nerve does receive fibers from the cervical sympathetic nerves. The three main branches are the ophthalmic, maxillary and mandibular. The latter two supply the side of the face, salivary glands, ear, mucous membrane of the mouth, pharynx and sinuses. The ophthalmic division (fig 1) consists of three segments, nasociliary, frontal and lacrimal, all of which pass through the superior orbital fissure into the orbit.

The nasociliary nerve is known as the nonvisual sensory nerve of the eyeball, which it innervates by its long and short ciliary branches.

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Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

1 Knowles, L C. Herpes Zoster. Report of 286 Cases, with Review of Unusual Features of the Disease, *Pennsylvania M J* **15** 615, 1911-1912.

2 Gunderson, T. Herpes Corneae, *Arch Ophth* **15** 225 (Feb) 1936, Convalescent Blood for Herpes, *Tr Am Ophth Soc* **33** 508, 1935, Convalescent Blood for Treatment of Herpes Zoster Ophthalmicus, *Arch Ophth* **24** 132 (Jul) 1940.

This nerve also supplies the inside of the nose and terminates as the infratrochlear branch, which is the sensory nerve for the nasal portion of the conjunctiva and the lateral aspect of the nose. The frontal nerve divides into two branches, the supratrochlear and the supraorbital, which supply the upper eyelid, the forehead and the scalp above the orbit. (Herpetic infections of the trigeminal nerve most frequently involve these two branches.) The lacrimal nerve courses along the temporal side of the orbit, it gives branches to the lacrimal gland and the lateral aspect of the conjunctiva and upper lid. It has frequent anastomoses with branches of the maxillary nerve.

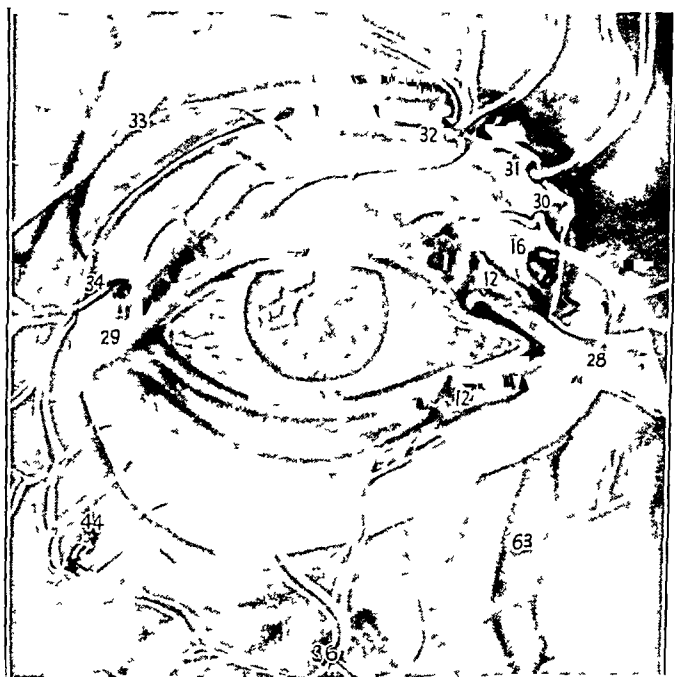


Fig 1—Sensory nerve supply to the orbital region beginning clockwise at the outer canthus 34, lacrimal nerve, 33, zygomatic-temporal branch of the maxillary; 32, supraorbital, 31, supratrochlear, 30, infratrochlear, 36, infraorbital, and 44 zygomaticofacial (the last two are branches of the maxillary) (Kronfeld, P. C., and McHugh, G. *The Human Eye*, Rochester, N. Y., Bausch and Lomb Press, 1943.)

CLINICAL FEATURES

Herpes zoster ophthalmicus may occur at any age and involves the sexes equally. It is not as serious in young persons because it is less painful and complications are not as frequent or prolonged. The prodromal symptoms are similar to those of any systemic infection. Unilateral neuralgic pain is the first characteristic sign and may precede the cutaneous eruption by several days. As the disease progresses vesicles develop which may become pustular, occasionally hemorrhagic or even

gangrenous. This active phase may last several weeks, but the ulcerated and gangrenous types are of longer duration. Hyperesthesia and neuralgic pains may persist for many months. There is usually an associated regional lymphadenitis with swelling of the upper eyelids.

Ocular complications are serious and occur in from 36 to 68 per cent (average 50 per cent)³ of those with herpes zoster ophthalmicus. The commonest ocular complication is keratitis which may be either superficial or deep. The former begins as minute transparent vesicles which rupture and form superficial ulcerations and are subject to secondary infections. The latter occurs as deep infiltrates within the cornea.

Next in frequency to corneal complications is involvement of the uveal tract, most commonly iritis. This produces photophobia, severe pain and disturbed vision. Examination reveals a small pupil, conjunctival hyperemia, a cloudy iris and sometimes a moderate increase in ocular tension. Involvement of the sclera alone is unusual. Ocular complications occur more frequently when the nasociliary nerve is involved and also when corneal anesthesia is present. Occasionally involvement of the ciliary ganglion produces an alteration in the pupil of the Argyll-Robertson type.

Complications involving the appendages of the eye are not usually as serious. The conjunctiva may remain red and somewhat swollen for several months. Some of the more unusual sequelae are those of exophthalmos and sympathetic ophthalmia. Paralysis of the extraocular muscles is uncommon, two theories are proposed for the cause of this complication. The first is that there is an extension of the inflammation from the nucleus of the fifth nerve to the motor nuclei. The other is that hemorrhages occur within the muscles as a result of inflammation and thrombophlebitis. Motor complications are generally late in their occurrence. The prognosis is favorable, but recovery may be delayed many months.

CAUSATION

Most observers agree that there are two types of herpes zoster, namely, the epidemic and the symptomatic types. In the first there appears to be a specific type of infection, probably virus in nature. The symptomatic type is usually secondary to a metabolic disturbance or is a complication of an acute or chronic infection. It may also follow trauma, neoplastic invasion and toxic conditions, such as metal poison-

3 Moore, R. F. Ocular Manifestation of Lesions of the Fifth Cranial Nerve. *Brit. M. J.* 2: 783, 1932. Bahnemann, H. J. Involvement of Conjunctival Bulbi in Herpes Zoster Ophthalmicus, *Inaug. Dissert.*, Würzburg, 1937. Edgerton, A. E. Herpes Zoster Ophthalmicus, *Arch. Ophth.* 34: 40 (July) 1945.

4 Brain, R. T. Relationship Between Viruses of Zoster and Varicella as Demonstrated by Complement-Fixation Reactions, *Brit. J. Exper. Path.* 14: 67, 1933.

ing In these instances the usual prodromal symptoms of infection and fever are absent, but the eruption is the same

Trauma is known to be an exciting factor, especially injuries to the head or surgical trauma to the region of the gasserian ganglion The relationship to chickenpox has stimulated some controversy as histologic sections of the vesicular lesion of both diseases are similar Varicella, however, can be transmitted to all susceptible hosts but herpes zoster only occasionally to infants Many instances have been reported in which herpes zoster has occurred in adults who were taking care of children with chickenpox Lipshutz and Kundratitz⁵ have reported on the successful transmission of the herpes zoster virus Goodpasture and Anderson⁶ have cultured the virus on skin grafted to a chick embryo Many workers⁷ have found that a specific antibody is contained in the serum of patients convalescing from herpes zoster, which also agglutinates the elementary bodies found in varicella vesicles

PATHOGENESIS

Head and Campbell⁸ in 1900 reported detailed observation on the posterior root ganglion, the peripheral nerves and the spinal cord of 23 patients who died during the course of herpes zoster Depending on the stage of the infection, the posterior roots showed varied changes, from acute hemorrhagic inflammation to degenerative changes These variations were also evident in the peripheral nerves and the posterior columns of the cord In most instances complete or partial regeneration of the ganglion and nerve took place Head and Campbell compared the changes of the posterior root ganglion with those found in the anterior horn cells in poliomyelitis, in all their cases, however, the anterior roots were found to be normal From their pathologic studies, they reached the following conclusions (1) Herpes zoster is the result of a lesion of the posterior root or nerve ganglion, (2) the pathologic changes that occur vary from acute inflammation to chronic scar forma-

5 Lipshutz, B Investigation on Etiology of Diseases of Herpes Group, *Arch f Dermat u Syph* **136** 428, 1921 Kundratitz, K *Experimentelle Uebertragungen von Herpes Zoster auf Menschen und die Beziehungen von Herpes Zoster zu Varicellen*, *Ztschr f Kinderh* **39** 379, 1925

6 Goodpasture, E W, and Anderson, K Infection of Human Skin Grafted on the Choriallantois of Chick Embryos with the Virus of Herpes Zoster, *Am J Path* **20** 447, 1944

7 (a) Netter, A, and Urbain, A Zonas varicelleux, anticorps varicelleux dans le serum de sujets atteints de zona, anticorps zosteriens et anticorps varicelleux dans le serum de sujets atteints de varicelle, *Compt rend Soc de biol* **90** 189, 1924 (b) Amies, C R Elementary Bodies of Zoster and Their Serological Relationship to Varicella, *Brit J Exper Path* **15** 314, 1934

8 Head, H, and Campbell, A W Pathology of Herpes Zoster and Its Bearing on Sensory Localization, *Brain* **23** 353, 1900

tion, (3) in cases of symptomatic or secondary herpes zoster the changes were the result of a vascular rather than infectious lesion with secondary destruction of the ganglion cells, and (4) the cutaneous eruption is undoubtedly produced by the intense irritation of the sensory cells within the ganglion which results in trophic changes in the cutaneous nerves. Other investigators⁹ have expressed the belief that herpes zoster is due to an ascending neuritis and secondary involvement of the ganglion. Wohlwill¹⁰ is of the opinion that the cutaneous eruptions are produced by a vasomotor reaction as a result of the infection spreading from the ganglion to the sympathetic fibers supplying the affected region. The present consensus of virologists¹¹ regarding herpes zoster is that it is a disease produced by a virus closely related to that of varicella. This virus can remain latent in the tissues and produce clinical zoster following various types of trauma, and it can be transmitted to susceptible persons. The mechanism and site of infection along with the reason for the neuritis and localization are yet unknown.

The cutaneous pathologic change consists of edema with the formation of septate vesicles within the epidermis, as the result of "ballooning degeneration." These epidermal cells contain basophilic nuclei and occasionally small eosinophilic bodies formerly believed to be inclusion bodies. Recent workers,¹² by utilizing the electron microscope, have been able to study these bodies more in detail and find a resemblance in the bodies occurring in variola and in vaccinia lesions. There is, however, some variation between these and the bodies seen in varicella, but the latter resemble those present in zoster and other pox diseases. The stratum corneum shows all the characteristics of inflammation, edema and vascular dilatation, with inflammatory and degenerative changes occurring in the vessel walls. There is usually a perivascular cellular infiltration. Nerves in the corium show swelling of the neurilemma and degeneration of the myelin sheath. Campbell and Head stated the belief that the corneal lesions were due to a subepithelial infiltration about terminal nerve endings which occasionally developed into vesicles.

The spinal fluid is altered in herpes zoster, the changes indicate a mild inflammatory reaction, increase in the cellular elements and a slight elevation in the albumin and globulin content.

9 Montgomery, D. W., and Culver, G. D. A Comparison Between Zoster of the Face and That of the Leg as Shown in Two Cases Recently Observed. *J. A. M. A.* 60:1692 (May 31) 1913.

10 Wohlwill, F. Zur pathologischen Anatomie des Nervensystem beim Herpes zoster, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 89:171, 1924.

11 Blank, H. Personal communication to the author.

12 Nagler, F. P. O., and Rake, G. The Use of the Electron Microscope in Diagnosis of Variola, Vaccinia, and Varicella, *J. Bact.* 55:45 (Jan.) 1940.

PROGNOSIS

The prognosis in any case of herpes zoster ophthalmicus must be guarded, especially when ocular complications occur. Corneal opacities, iridocyclitis, secondary glaucoma and occasionally perforation of the cornea may result. Neuralgic pains with hyperesthesia of the cornea may be severe and persistent.

DIFFERENTIAL DIAGNOSIS

Erysipelas, supraorbital neuralgia, frontal sinusitis, migraine headaches, contact dermatitis, impetigo and herpes simplex are the commonest entities to be considered. Differentiation between herpes zoster and herpes simplex in certain cases is difficult, especially when the cornea is involved. A definite decision can be made by inoculation of a rabbit's cornea. Injection of vesicular fluid from herpes simplex usually produces typical keratitis and encephalitis, whereas material from the vesicles of herpes zoster does not. Serum of patients convalescing from herpes zoster gives a complement fixation reaction with an antigen prepared from herpes zoster vesicular fluid,¹³ while material from herpes simplex does not.

TREATMENT

The treatment remains symptomatic, bed rest, the use of analgesics and large doses of thiamine chloride have been recommended. Rest of the eye is paramount, and when there is evidence of iritis treatment with mydriatics is indicated. Roentgen therapy to the gasserian ganglion has been utilized, as have repeated smallpox vaccinations,¹⁴ injections of diphtheria antitoxin¹⁵ and other nonspecific foreign protein agents.

Friedenwald¹⁶ in 1929 was the first to use convalescent serum. In 1935 Gunderson² reported the use of convalescent blood in the treatment of 10 patients with herpes zoster ophthalmicus. He observed that the results were encouraging, especially when the patients were treated early in the infection and prior to corneal involvement. There was prompt alleviation of pain, and in others the period of morbidity was shortened and impairment of vision was lessened. His second report in 1940 was on a total of 91 patients, 51 (60 per cent) of whom had definite eye involvement. Some of these patients were treated with transfusions of blood obtained from patients who had recovered from herpes zoster. Eighty-two per cent of those so treated retained useful vision 6/18 or

13 Brain⁴ Goodpasture and Anderson⁶

14 Lillie, W. I. Therapy of Herpes Ophthalmicus with Smallpox Vaccine, *New York State J. Med.* **43** 857, 1943.

15 Thomas, W. P. Diphtheria Antitoxin and Other Foreign Proteins in Therapy of Herpes Zoster Ophthalmicus, *J. M. A. Georgia* **36** 82, 1947.

16 Friedenwald, J. S. Report of Case of Herpes Zoster Ophthalmicus Treated with Convalescent Serum, *Bull. Johns Hopkins Hosp.* **45** 193, 1929.

better. In the 39 control patients who did not receive blood, only 60 per cent were as fortunate. He advised giving 250 to 450 cc of convalescent blood, preferably early in the disease. It is my purpose to report on 5 patients who were treated in this manner with better than average results.

REPORT OF CASES

CASE 1 (fig 2)—U. M., a white man 48 years of age, was seen in consultation with Dr. John Powers. One week before, his present illness had begun with sharp shooting pains involving the right side of his forehead. On Sept. 3, 1940, physical examination revealed a temperature of 101 F, edema of his right eyelid and hemorrhagic grouped vesicles covering the right side of the forehead, upper eyelid and side of the nose. Severe blepharospasm was present, and several



Fig 2 (case 1)—Herpes zoster ophthalmicus. Vesicles along the side of the nose, indicating involvement of the nasociliary nerve, may be noted.

pinhead-sized vesicles were situated on the cornea between 5 and 7 o'clock. On September 5 and 7 the patient received two 450 cc blood transfusions from two donors, each of whom had had thoracic herpes zoster six months previously. Dr. Powers reported on the status of the cornea as follows: On September 5 there were several small ulcers of the cornea and staining; on September 9, the ulcers were shallower, with less staining present; on September 12, there was no staining but the fundus was hazy; on September 13 there was congestion about the limbus, but no staining present; on September 20, the eye was clear and vision normal (fig 3). A striking decrease in pain, eyelid edema and cutaneous inflammation followed the first transfusion. The temperature slowly became normal by September 7.

CASE 2—Mrs. M. De, a white woman 63 years of age, was admitted to St. Mary's Hospital on June 22, 1941, with a history of general malaise and fever for

the previous week. Four days before a vesicular eruption of the forehead, cheek, nose and palate had developed, which was associated with severe sharp pains in the left side of the face and left eye. The admission temperature was 102 F, an erythematous vesicular eruption was present in the painful areas. The left eyelid was swollen but otherwise normal. Four days later the patient was seen by Dr K. R. Fawcett, who noted severe photophobia, a swollen conjunctiva but a clear cornea. At this time several more vesicles were present along the tip of the nose. On the next day a transfusion of 450 cc of whole blood was given from one of the donors used in case 1. The following day the edema of the eye and pain were decreased and the temperature dropped to normal. On June 30 the eye was irritable, the pupil was irregular and photophobia was severe. These observations were suggestive of early iritis. Another 450 cc transfusion was given on July 2,

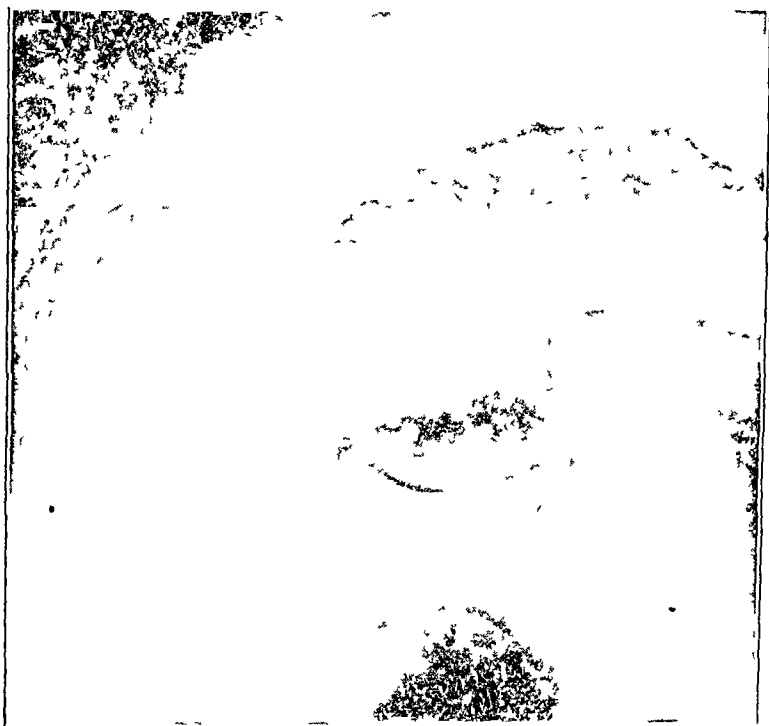


Fig 3 (case 1)—Photograph taken fourteen days after figure 2, the patient had received two transfusions of convalescent blood, the cornea is clear, and the edema and cutaneous eruption have subsided.

after this the patient continued to improve. Normal vision was present at the time of discharge.

CASE 3—E. H., a 67 year old white man, was admitted to St. Mary's Hospital Nov. 29, 1946, with one week's history of fever, malaise and pain on the right side of his head. Three days prior to admission the right eyelids became swollen and a vesicular eruption appeared on the right eyelid, forehead and side of the nose. At the time of admission the eye was swollen shut. Dr. K. R. Fawcett observed that the cornea was clear, but the presence of nasal vesicles indicated involvement of the nasociliary nerve. The following day the patient was given 300 cc of whole blood from a donor who had had thoracic herpes several months previously. The day thereafter the temperature, which had risen to 101 F daily, was normal, pain

and edema were greatly reduced. When the patient was discharged, on December 4, his eye was clear and he was free from pain. His vision was normal.

CASE 4—A 79 year old woman¹⁷ was admitted to St Luke's Hospital May 26, 1944, complaining of pain in the left eye and the left ear, a sore throat and malaise of nine days' duration. Two days before hospital admission, a vesicular eruption had appeared along the left eyelid, forehead and scalp, associated with nausea and vomiting. Examination on admission revealed that the left eyelids were closed and hemorrhagic vesicles covered these areas. Two roentgen treatments of 150 r each were given to the gasserian ganglion on May 26 and 29. Examination on May 27 and 29 showed that the cornea was clear, but on June 1 pinpoint corneal ulcers were evident. On June 3, 200 cc of blood plasma from a patient who had previously had herpes zoster was given intravenously. After this, the pain lessened and the ulcers showed evidence of healing. On June 7, the cornea was again clear and remained so.

CASE 5—J E, a boy 12 years of age, was admitted to St Mary's Hospital on July 12, 1946. He had been ill one week. Examination revealed intense swelling of the eyelids and a vesicular eruption on the right upper lid and side of the nose. The temperature was 103 F. Examination of the globe, though difficult because of blepharospasm, revealed no abnormality. Twenty cubic centimeters of blood obtained from the donor in case 3 was given in each buttock on July 13. The following day, the temperature was 100.6 F, the next day it was normal. No corneal involvement occurred, and he was discharged July 17.

CONCLUSION

In general most therapeutic measures advocated for herpes zoster are based on initiating a nonspecific foreign protein reaction. Evidence favors some sort of a virus infection, because recurrences are unusual and inclusion bodies are present in the vesicles. Antibodies have been found in the serum of convalescent patients. Rivers¹⁸ has stated that convalescent blood or serum is of no value in the therapy of virus diseases, because by the time the disease is evident the organism has already penetrated the cell, a barrier which no antibody can transgress. Amies^{7b} found elementary (inclusion) bodies in zoster vesicles twenty-four to forty-eight hours after development and that agglutinins were not demonstrable until the third week of the disease. It seems reasonable that convalescent blood may be of aid in this infection because of delayed development of inclusion and antibodies. Most patients with this affliction are past middle age, and their general well-being may be enhanced by a blood transfusion. Whatever the mechanism may be, it is my opinion that the convalescent blood is of value particularly when given early, prior to eye involvement. After this treatment the temperature usually becomes normal, pain is alleviated, the edema and inflammation are decreased, the ophthalmic lesions begin to heal and the

¹⁷ Reported with the permission of Dr R J Eckman and Dr J E Powers.

¹⁸ Rivers, T M. *Viruses and Virus Diseases*, Stanford University, Calif, Stanford University Press, 1939.

patient in general feels better and is decidedly less toxic. Gunderson's excellent results also support this method of therapy. It is therefore apparent that until a better agent is devised injection of convalescent blood or serum is beneficial in treatment of patients with herpes zoster ophthalmicus when (1) the patient is debilitated, especially if he is over 50 years of age, (2) conjunctival edema is present, (3) corneal anesthesia is present, (4) the infection involves the nasociliary nerve, indicated by vesicles occurring along the sides of the nose, or (5) any involvement of the globe occurs.

SUMMARY

The two types of herpes zoster ophthalmicus are the epidemic and the symptomatic. The clinical features of herpes zoster ophthalmicus and the ocular complications which ordinarily occur in 50 per cent of the cases are considered. Gunderson's treatment with convalescent blood transfusions is discussed, and reports on 5 patients who benefited by this therapy are given.

ADDENDUM

Since submitting this paper I have treated satisfactorily a 72 year old woman (a patient of Dr. A. C. Hilding) with involvement of the right eye and corneal ulcerations. In this instance two intravenous injections of 250 cc. of convalescent serum was used because of Rh factors.

ABSTRACT OF DISCUSSION

DR. O. S. PHILPOTT, Denver. I first heard of this method of treatment about ten years ago from an ophthalmologist colleague, but have had no personal experience with its use. My interest in immunotransfusions for various conditions makes me welcome the opportunity to discuss Dr. Becker's paper. My experience leads me to assume a virus as the cause of herpes zoster, and this assumption is confirmed, I think, by my reading, particularly since Kunderatitz produced a varicella-like eruption in young children by inoculating the skin with fluid taken from an adult with herpes zoster. I have at times testified in compensation hearings that trauma can be the trigger mechanism which incites an attack of herpes zoster. To reconcile the idea that herpes is of virus causation sometimes produced by trauma, one may assume that the virus lies dormant in some persons for years, in children, it is capable of producing in certain circumstances, varicella where the integument is the organ of major involvement. In adults, in other circumstances, it is capable of producing a limited herpetic eruption with the nerve ganglion and posterior roots bearing the primary pathologic process.

Because there has been until the present no specific remedy for herpes zoster, each of us tries many things and comes at last to adopt a method which in his hands proves the most successful. Since the report in the 1936 "Year Book" of Danow I have advocated oral and intravenous use of large doses of freshly prepared cevitic acid. Now, because of Dr. Becker's recommendation, I am eager to try the therapy which he has detailed.

I would like to ask Dr. Becker whether he has any suggestions as to which period in convalescence is the best time to take blood from the donor. This request is based on some investigations I made while using convalescent serum in

the treatment of erysipelas. It was my conclusion that convalescent blood taken from patients about six months after recovery contained the highest titer of therapeutic value. Of course, erysipelas is a bacterial disease with some tendency toward recurrences, while herpes zoster is a virus disease usually conferring lifetime immunity.

In reading the bibliography appended to Dr. Becker's paper I was impressed by the references to ophthalmologists. I have repeatedly found in the literature, on subjects in which our interests overlap, that much of the original work has been done by them. Recently I looked up the association of nevus flammeus with glaucoma, I could find no references in dermatologic literature, but there were several in ophthalmologic journals. I find myself frequently indebted to them for aid.

DR. JAMES W. BURKS JR., New Orleans. Not only has Dr. Becker given an excellent review of the present knowledge of herpes zoster but he has confirmed Gunderson's success in the use of convalescent serum in the treatment of this disease. Results of treatment of herpes zoster of the eye, in which 50 per cent of the patients have some loss of vision, are more readily evaluated than results in cases in which the disease involves anatomic sites resulting mainly in subjective symptoms. Until recently theoretic difficulties, such as inability of antibodies to penetrate cells to bind viruses, have prevented direct approach to the specific therapy of virus diseases. These results obtained by Dr. Becker, along with certain chemotherapeutic results obtained by others through the administration of sulfonamide compounds and of penicillin in certain virus and rickettsial diseases, might suggest that such a direct approach is not out of the question. Such favorable therapeutic responses may be due to the prevention of multiplication of the viruses or to some change in the resistance of the cells. Therefore, as Dr. Becker pointed out in his paper, treatment with convalescent serum, if it is to be effective, must be instituted early in the disease.

I have used chromium sulfate grains, 12 daily for five days, in the treatment of herpes zoster and herpes simplex with some success. This drug was formerly used in the treatment of various neurologic conditions.

After reading Dr. Becker's paper I treated a patient with herpes ophthalmicus with convalescent serum. This patient's symptoms had been present for three days. Changes in the skin had appeared twenty-four hours previously. Twenty cubic centimeters of whole blood obtained from a donor who had recovered from herpes ophthalmicus three months before was given in the buttocks. Both objective and subjective improvement was noted the following day. Involution has continued and his vision has not been affected.

DR. FREDERIC T. BECKER, Duluth, Minn. In answer to one question which was asked, about the most advantageous time to obtain donor's blood, Ames found that the titer of the agglutinins reached their height about three weeks after the infection, and they were present in a high titer for several years. The difficulties encountered in finding the inclusion bodies have been discussed in a paper not yet published by Rake and his co-workers. They found that twelve hours after the vesicle develops is the most opportune time to obtain the inclusion bodies. After ninety-six hours, they are greatly decreased and agglutinated. One theory they have proposed in explanation of this early agglutination is that most persons have some immunity due to a previous attack of chickenpox. I would suggest using a donor any time from three weeks up to two years after the infection.

EXAMPLES OF CROSS SENSITIZATION IN ALLERGIC ECZEMATOUS DERMATITIS

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THE SUBJECT of cross sensitization in allergic eczematous contact type dermatitis has been considered by many investigators. One of the first examples of a study on cross sensitization in allergic eczematous dermatitis was Bloch's investigations in 1911¹ on the nature of iodoform hypersensitivity. From this study he concluded that in his cases the hypersensitivity of the cutaneous cells was not directed against free iodine but against methyl and methane groups. Bloch's observations and conclusions have since then been extended. For it is known today that there are various forms of iodoform hypersensitivity: in some cases the hypersensitivity probably can be directed against the free iodine, which is split off, in others, against the whole iodoform (tri-iodo-methane) molecule or against iodine-substituted methanes or in still other cases against any substituted or unsubstituted methane or methyl groups (Sulzberger²). Bloch's classic study showed that certain cases of multiple sensitizations which might have been classified as polyvalent, although specific, actually represented cross sensitizations among a number of chemically and hence immunologically related compounds. Moreover, his study explained the previously puzzling fact that some patients experienced specific allergic sensitizations to agents which they had never previously encountered as such.

Many further studies on cross sensitization have been carried out since Bloch's study and some of these and their implications are discussed by Sulzberger². In this report I shall limit myself to a discussion of cross sensitizations among a group of compounds which with few exceptions contain aromatic amines as part of their molecule. Studies on cross sensitizations among these compounds are by no means new,

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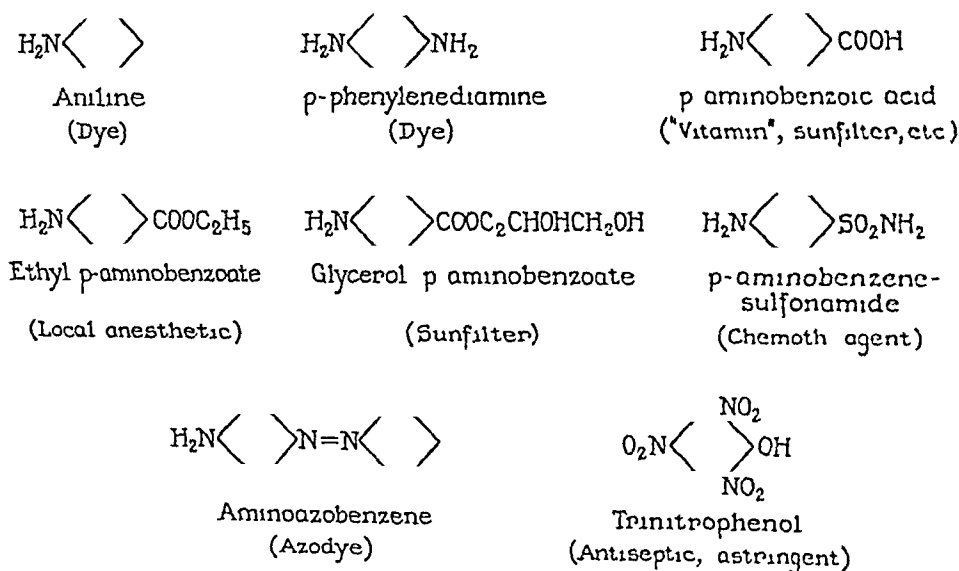
From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, Post-Graduate Medical School of the New York University-Bellevue Medical Center (Dr. Marion B. Sulzberger, Director).

1 Bloch, B. Experimentelle Studien ueber das Wesen der Jodoformidiosynkrasie, *Ztschr f exper Path u Therap* 9 509, 1911.

2 Sulzberger, M. B. *Dermatologic Allergy*, Springfield Ill., Charles C. Thomas, Publisher, 1940.

but are of renewed interest at the present time because of the ever increasing opportunities for exposures to aniline derivatives

An excellent clinical example of such a cross sensitization to certain aromatic amines is that of R R, a man aged 43, whose case was reported in detail by Meltzer and Baer.³ A sensitization to benzocaine (ethyl-para-aminobenzoate) was discovered in this patient in 1939. Subsequently, while in North Africa with the United States Army in 1944, he was invited to a sheik's dinner and, to "prevent undesirable gastrointestinal after effects from the meal," took a sulfonamide drug, probably sulfaguanidine (para-amino-benzenesulfanylguanidine). The ingestion of the sulfonamide drug was followed by a severe vesicular eruption on the palms and soles. In March 1947, while in Florida, and in July 1947, while on a cruise he had vesicular eruptions on the



Representative compounds which produce reactions in patient R R

hands, which were traced to the use of a sunburn preventive lotion containing glycerol para-aminobenzoate as a sun-filtering agent

Further patch testing to detect other cross sensitizations in this patient showed him to be allergic to a number of related substances. Among those to which he gave strong reactions were several local anesthetics which are derivatives of para-aminobenzoic acid, sulfanilamide, paraphenylenediamine and aniline, weaker reactions were noted to certain azodyes and also to picric acid (figure)

CROSS SENSITIZATIONS AMONG CERTAIN LOCAL ANESTHETICS

Cross sensitizations among local anesthetics, a number of which were noted in the aforementioned patient, R R, have been studied for

³ Meltzer, L., and Baer, R. L. Sensitization to Monoglyceryl Para-Aminobenzoate, *J Invest Dermat* 25, 1948

many years and have recently been reviewed by a number of authors (Rothman, Orland and Flesch,⁴ Strauss⁵ and Meltzer and Baer³)

Within this relatively small group of compounds several types of cross sensitizations have been reported which vary not only in width of the sensitization spectrum but also are based on different mechanisms. The chemical groups on which the cross sensitizations reported in the literature were based are the following (a) aniline (Goodman⁶), (b) an-OH group in the para or meta position on an aminobenzene ring (Schwarzschild⁷), (c) a tertiary amine (James⁸), (d) benzoic acid with a tertiary amine in the side chain (Waldron⁹), (e) esters of para-aminobenzoic acid with secondary or tertiary amines in the side chain (Rothman and his co-workers⁴) and (f) alkyl esters of para-aminobenzoic acid (Laden and Rubin¹⁰)

CROSS SENSITIZATIONS AMONG CERTAIN LOCAL ANESTHETICS AND PARA-PHENYLENEDIAMINE

This type of cross sensitization has been studied mainly in France by Flandin, Rabeau and Ukrainczyk,¹¹ who described it as "sensitization to various substances containing a primary amino group in the para position," and later by Tzanck¹² and Sidi¹³. Such cross sensitization was noted in the aforementioned patient, R. R. Another very instructive case of this type is a patient of Tzanck's, who, after a widespread dermatitis due to application of picric acid for shingles developed,

4 Rothman, S., Orland, F. J., and Flesch, P. Group Specificity of Epidermal Allergy to Procaine in Man, *J Invest Dermat* **6** 191, 1945

5 Strauss, M. J. Group Sensitivity to Local Anesthetics. Confirmation of the Possibility of Its Occurrence and Demonstration that It Does Not Necessarily Always Take Place, *J Invest Dermat* **8** 403, 1947

6 Goodman, M. H. Cutaneous Hypersensitivity to Procaine Anesthetics, *J Invest Dermat* **2** 53, 1939

7 Schwarzschild, L. Sensibilisierungsversuche aus der Orthoformreihe, *Arch f Dermat u Syph* **156** 432, 1928

8 James, B. Procaine Dermatitis. Report of Case and Attempt to Determine Chemical Groups Responsible for Hypersensitiveness, *J A M A* **97** 440 (Aug 15) 1931

9 Waldron, G. W. Hypersensitivity to Procaine, *Proc Staff Meet, Mayo Clin* **9** 254, 1934

10 Laden, E. L., and Rubin, L. Specificity of Eczematous Hypersensitivity to Para-Aminobenzoic Acid Butyl Ester (Butesin), *Proc Soc Exper Biol & Med* **66** 451, 1947

11 Flandin, C., Rabeau, H., and Ukrainczyk. Intolerance a certains anesthesiques synthetiques et a l'aniline, *Bull Soc franc de dermat et syph* **43** 1638, 1936

12 Tzanck, R. M. Accidents cutanes par sensibilisation a diverses substances contenant toutes une fonction amine primaire substituee en position para. Paris, Librairie Louis Arnette, 1942

13 Sidi, E. Les accidents cutanes des teintures capillaires, Editions Medicales Flammarion, 1945

suffered successively through the years from a widespread dermatitis after application of a local anesthetic in an ointment for hemorrhoids, a dermatitis of the upper lip after he had dyed his moustache with a dye which apparently contained paraphenylenediamine or a closely related compound, a dermatitis of the face after receiving local anesthesia for dental work and a dermatitis of the scrotal region after application of a salve containing cocaine for epididymitis. Tzanck also cited the case of a beauty parlor operator who had dermatitis of the hands due to paraphenylenediamine hair dyes and who had a severe flare-up after the dentist used procaine hydrochloride in her mouth. Sidi called attention to the interesting fact that while the large majority of his patients who were hypersensitive to local anesthetics were also hypersensitive to paraphenylenediamine, only a few of his paraphenylenediamine-hypersensitive subjects showed cross sensitization to local anesthetics. This would indicate that the tendency to this form of cross sensitization is greater when the primary sensitization takes place to certain local anesthetics than when the primary sensitization takes place to paraphenylenediamine.

CROSS SENSITIZATIONS AMONG CERTAIN LOCAL ANESTHETICS AND SULFONAMIDE DRUGS

Relatively little is known about this type of cross sensitization. Phillips'¹⁴ studies revealed that among subjects suffering from dermatitis due to various sulfonamide drugs 68 per cent reacted to cutaneous tests with sulfanilamide, 30 per cent to sulfapyridine, 21 per cent to sulfathiazole, 11 per cent to sulfaguanidine and 7 per cent to sulfadiazine, while 16 per cent reacted to procaine hydrochloride, thus shows that in a group of subjects hypersensitive to sulfonamide drugs the incidence of hypersensitivity to procaine hydrochloride is greater than to sulfaguanidine and sulfadiazine. Sulzberger, Kanof and Baer¹⁵ observed cross sensitization to para-aminobenzoic acid in 2 of 8 subjects with dermatitis due to sulfonamide drugs, and 1 of these subjects also reacted to procaine hydrochloride. Another highly instructive case is described by Rogers¹⁶, his patient, after taking sulfanilamide, experienced dermatitis in all those sites which had years before, at various times, been involved with sensitization dermatitis due to pro-

¹⁴ Phillips, B. A Clinical Study of Sulphonamide Dermatitis, *Brit J Dermat* 58 213, 1946

¹⁵ Sulzberger, M. B., Kanof, A., and Baer, R. L. Sensitization by Topical Application of Sulfonamides, *J Allergy* 182 92, 1947

¹⁶ Rogers, E. B. Sensitization Reaction to Sulfanilamide, *J A M A* 111 2290 (Dec 17) 1938

came hydrochloride, tutocaine hydrochloride[®] (butamin hydrochloride, no longer marketed) and butacaine sulfate. In the aforementioned case of R R the dermatitis due to sulfonamide drugs also occurred after a preceding sensitization to the local anesthetic ethyl aminobenzoate.

Despite these reports on sensitizations due to sulfonamide drugs with a rather wide sensitization spectrum crossing over to para-aminobenzoic acid and its derivatives, it must be remembered that in some cases the sensitization due to sulfonamide drugs appears to be more specific, as exemplified by the case of Davidson and Bullowa.¹⁷

CROSS SENSITIZATIONS AMONG CERTAIN DERIVATIVES OF NITROBENZENE AND OF ANILINE

It is nowadays generally accepted that nitro groups can be reduced in the human tissues to amino groups (Lipschitz¹⁸). The possibility that the skin is capable of reducing nitro groups to amino groups has also been considered for many years. This reduction process in the skin explains the cross sensitizations observed clinically between certain derivatives of nitrobenzene and aniline. I have already mentioned the patient of Tzanck,¹² in whom dermatitis due to picric acid (trinitrophenol) first developed and then cross sensitizations to certain local anesthetics and paraphenylenediamine. Sidi¹³ cited cases of cross sensitization to picric acid and paranitrophenol in patients with paraphenylenediamine hypersensitivity. A relatively weak cross sensitization to picric acid was also present in the aforementioned patient R R.

However, Dr S Dobkevitch and I tested 10 subjects strongly hypersensitive to paraphenylenediamine with picric acid and did not observe any cross sensitizations. From these few available reports, it can be concluded that cross sensitization among certain derivatives of nitrobenzene and of aniline may occur, but that such cross sensitization is not common.

CROSS SENSITIZATIONS AMONG PARAPHENYLENEDIAMINE AND AZODYES

This type of cross sensitization was first described and explained by Mayer¹⁹ and has recently again taken on practical importance because of the not infrequent occurrence of dermatitis due to azodyes in "nylon" stockings with cross sensitization to paraphenylenediamine.

17 Davidson, A, and Bullowa, J G M. Acquired Hypersensitivity to Sulfapyridine and Sulfamethylthiazole, *New England J Med* **223** 811, 1940.

18 Lipschitz, W. Mechanismus der Giftwirkung aromatischer Nitroverbindungen, zugleich ein Beitrag zum Atmungsproblem tierischer und pflanzlicher Zellen, *Ztschr f physiol Chem* **109** 189, 1920.

19 Mayer, R L. Die Ueberempfindlichkeit gegen Koerper von Chinonstruktur, *Arch f Dermat u Syph* **156** 331, 1928.

as described by Dobkevitch and Baer²⁰ A very weak cross sensitization of this type was noted in the aforementioned patient, R R It is based on the fact that both substances undergo transformations in the skin which lead to the formation of the same intermediate compounds Moreover, Baer, Leider and Mayer²¹ were able to show that this type of cross sensitization probably also extends to some of the azodyes which in the United States are certified for use in foods, drugs and cosmetics Whether this probable cross sensitization among certified azodyes and paraphenylenediamine is of actual clinical importance has not yet been adequately investigated, but an investigation is being pursued by the same workers

COMMENT

The term cross sensitization as employed here refers to the phenomenon in which a given sensitization crosses over among several compounds (1) because they contain the identical alleiogenic principle and (2) because the sensitization with, and against, a certain eczematogenic alleiogen indeed produces allergic eczematous contact type sensitization not only to itself (primary alleiogen and primary sensitization) but also to one or more immunochemically related alleiogens (secondary allergens and secondary sensitizations)

Thus when the phenomenon of cross sensitization occurs, agents to which the skin has not previously been exposed may elicit an allergic dermatitis These cross sensitizations can be explained by the following possibilities of an immunochemical relationship between the primary and the secondary allergens

- 1 The "primary" alleiogen and the "secondary" alleiogen may be immunochemically so closely related (e g, contain identical alleiogenic groups) that the sensitized cells do not differentiate between them and thus react toward them as if they were identical (group specificity)

- 2 The "primary" alleiogen is converted (reduced, oxidized and the like) in the body into an agent which is identical with or so closely related to the "secondary" alleiogen that the sensitized cells do not differentiate between them

- 3 The "secondary" alleiogen is converted in the body into an agent which is identical with or so closely related to the "primary" alleiogen that the sensitized cells do not differentiate between them

20 Dobkevitch, S, and Baer, R L Eczematous Cross-Hypersensitivity to Azodyes in Nylon Stockings and Paraphenylenediamine, *J Invest Dermat* 9 203, 1947

21 Baer, R L, Leider, M, and Mayer, R L Possible Eczematous Cross-Hypersensitivity Between Paraphenylenediamine and Azodyes Certified for Use in Foods, Drugs and Cosmetics, *Proc Soc Exper Biol & Med* 67 489, 1948

4 Both the primary and the secondary allergens are converted in the body into agents which are either identical or are so closely related that the sensitized cells do not differentiate between them

These examples of direct cross sensitizations must be differentiated from indirect cross reactions which are produced by concomitant factors. Thus certain cross reactions (Landsteiner²²) may occur when a sensitizing compound contains, in addition to its principal allergen, one or more other substances with allergenic potential (e g, "contaminants") which themselves may give rise to independent sensitizations or elicit dermatitis in already sensitized skin

There is little doubt that cross sensitizations are of greater practical importance than is generally realized. With more widespread knowledge of the chemical relationship between substances and the cross sensitizations which can occur, one should be able to improve the practice of preventive medicine in allergic eczematous dermatitis. For example, it follows from the foregoing discussions that a patient who is known to have an allergic eczematous sensitization to paraphenylenediamine in a hair dye or to azodyes in "nylon" stockings should not have his skin painted preoperatively with picric acid or should not use a sunburn preventive containing glycerol para-aminobenzoate. Indeed, such a patient, even if he has not yet experienced cross sensitizations to the whole series of related substances, would certainly be more likely to experience a sensitization dermatitis to picric acid or glycerol para-aminobenzoate than would a "normal" subject, not hypersensitive to paraphenylenediamine.

Therefore, exposure to the whole groups of eczematogenic allergens or immunochemically related allergens should be avoided whenever possible, not only to avert recurrences of dermatitis but because it has been shown that repeated exposures to the specific allergen (or allergenic group²³) tend to increase the level of sensitivity (Witten and Shair²³), and clinical experience suggests that they also tend to widen the sensitization spectrum.

These cross sensitizations are furthermore of great interest because they may help to explain some cases when substances, which themselves have an extremely low sensitizing index, elicit severe sensitization dermatitis.

It is not intended here to suggest that a common immunochemical basis is responsible for all cases of multiple sensitizations. On the contrary, it must be stressed that there are a majority of cases of multiple

22 Landsteiner, K. *The Specificity of Serological Reactions*, Cambridge, Mass., Harvard University Press, 1945.

23 Witten, V. H., and Shair, H. M. *Repeated Patch Testing in Allergic Eczematous Sensitization*, *Ann. Allergy*, to be published.

sensitizations when no common denominator can be found and when one is justified in assuming that there has developed in the skin a specific allergic, nonspecific polyvalence of sensitization rather than a cross sensitization or, as it also has been called, a cross hypersensitivity or group hypersensitivity

Examples of true cross sensitizations other than those previously discussed are known to occur with various plants of the *thus* family, among the "oil" fractions of ragweed, burweed, marsh elder and pyrethrum (Feinberg²⁴ and Brunsting and Anderson²⁵), among various therapeutically used tars and so forth. However, from the practical and theoretic points of view, one of the most important, interesting and best studied cross sensitizations is that which occurs among various compounds containing aniline as part of their molecule. Their practical importance is best illustrated by the fact that one single primary sensitization may explain sensitizations to such seemingly diverse materials as aniline, paraphenylenediamine, para-aminobenzoic acid (a part of the vitamin B complex), certain local anesthetics, glycerol para-aminobenzoate, a now widely used "sun-filter," certain sulfonamide drugs and certain azodyes used in stockings, clothing, food, drugs and cosmetics.

SUMMARY

Examples of practical importance are presented of cross sensitizations between various compounds which contain aniline as part of their molecule. It has been shown that on the basis of a primary sensitization to a single agent a patient may through cross sensitization become hypersensitive to such a variety of compounds as aniline, paraphenylenediamine, para-aminobenzoic acid, certain local anesthetics, glycerol para-aminobenzoate, now widely used in sunburn preventives, certain sulfonamide drugs and certain azodyes used in dyeing stockings, clothing, foods, drugs and cosmetics.

Increased knowledge of the occurrence of cross sensitizations should be helpful in the practice of preventive medicine in eczematous dermatitis, as it makes possible the avoidance not only of the causal ("primary") allergen but, in addition, of the immunochemically related ("secondary") allergens. Moreover, in some cases they help to explain the basis for multiple sensitizations and the causation of sensitization dermatitis by compounds with ordinarily very low sensitizing indexes.

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24 Feinberg, S. M. Pyrethrum Sensitization Its Importance and Relation to Pollen Allergy, *J. A. M. A.* **102** 1557 (May 12) 1934

25 Brunsting, L. A., and Anderson, C. R. Ragweed Dermatitis Report Based on Eighteen Cases, *J. A. M. A.* **103** 1285 (Oct 27) 1934

ABSTRACT OF DISCUSSION

DR STANLEY F HAMPTON, St Louis Dr Baer has presented further evidence of cross sensitization between chemically related compounds. The results of his work are of most practical importance. Dr Baer has reviewed the literature in his manuscript. I want to mention two of his references to bring out special points.

Laden and Rubin showed sensitization to alkyl esters of para-aminobenzoic acid in a patient sensitive to butesin picrate but no sensitivity to derivatives of para-aminobenzoic acid with tertiary amines in the side chain, whereas Rothman, Orland and Flesch reported cross sensitization in a subject to para-aminobenzoic acid ester containing secondary or tertiary amines.

In the immediate wheal type or anaphylactic type of allergy, cross sensitization has been readily recognized, particularly in horse serum and horse-dander sensitive persons, in the ragweeds and other composite pollen antigens and among various grass pollen antigens. Stull and I found that the uterus of guinea pigs individually sensitized to timothy, June grass and orchard grass reacted in the Dale test to the other grass antigens and, in most instances, neutralized to the original sensitizing one. Sherman and Stull, using multiple sensitive serums in passive transfer, showed cross neutralization of not only botanically related antigens but also unrelated antigens, such as dog dander and hickory pollen. Antigens which reacted strongly with sensitive serums tended to neutralize antigens of less reactivity.

Probably the most distinctive examples of specificity in sensitization were reported by Sulzberger and Baer, by Landsteiner and Jacobs and by Rostenberg and Kanof in that mere rearrangement of chlorine groups on a nitrobenzene nucleus resulted in different, specific sensitivity. Aminophylline rectal suppositories are in common use today in the treatment of bronchial asthma. Some brands of suppositories contain ethyl aminobenzoate, the ethyl ester of para-aminobenzoic acid. Local pain, accompanying the use of such suppositories, has been occasionally observed and attributed to primary irritation of the aminophylline in cases of rectal lesions, such as fissures and proctitis. I wonder whether some of these reactions may not be due to sensitivity to ethyl aminobenzoate. I would like to ask Dr Baer about his experience in this regard and whether primary or cross sensitivities have been observed by him in the clinical use of rectal suppositories containing ethyl aminobenzoate.

DR ADOLPH ROSTENBERG, JR, Chicago Studies in cross sensitizations are of both theoretic and practical interest. On the theoretic side, such studies furnish information as to the importance of certain chemical groupings in determining immunologic specificity. Dermatologists can be proud of the eczematous sensitization, as it is a unique tool in this respect, for the conjugated antigens are made in vivo. A simple chemical, to become antigenic, either itself unites or some degradation product of it unites with a body constituent. Thus by properly selecting the chemicals, studies in cross sensitizations can furnish information as to the manner of breakdown of compounds as well as to their mode of uniting and finally as to antibody specificity.

On the practical side, such studies offer one the possibility of making prognostications concerning other substances to which a person may react. This then inevitably raises the question as to how far one can extrapolate from a given case. That is, given a person who is sensitive, say, to 2,4 dinitrochlorobenzene and having determined that that person is also sensitive to certain other compounds, how likely is it that another person sensitive to 2,4 dinitrochlorobenzene will also react to the other compounds as did the first person? In the state of

present knowledge, one cannot answer this query. This, in my opinion, is because the majority of studies concerning cross sensitizations have been made with 1 or 2 persons in whom sensitivities developed spontaneously.

I have elsewhere (*J. Invest. Dermat.* 6:201, 1945) considered the chief objections to such studies, and would like now to recapitulate the two most important: (1) a lack of knowledge on the part of the investigator concerning other related sensitizing substances to which the patient may have been simultaneously exposed and (2) a lack of knowledge regarding the biologic variability of the patient in question.

I realize that one is often constrained to use this type of study, but would like to take this occasion to make a plea for more studies in which the sensitizations are deliberately induced and, hence, various important immunologic factors controllable.

DR. RUDOLF L. BAER, New York: In answer to Dr. Hampton's question, I have seen dermatitis of the perianal region due to local anesthetics in suppositories, and cross sensitizations in these cases are probably not uncommon at all.

I agree with Dr. Rostenberg that, in order to study cross sensitizations it is, in some ways, much better for one to start with a compound of known chemical composition to which human beings are not normally exposed. Then there is good reason to assume that the patient previously has not been exposed to the same compound or closely related compounds and one knows when the patient first became sensitized. However, this does not eliminate the need for studying cross sensitizations with compounds when deliberate sensitizations would be inadvisable or impossible.

I mentioned cases in which strongly positive reactions to patch tests were elicited with dyes certified for use in foods, drugs and cosmetics. I would like to add that, in testing these compounds, one has to be careful in evaluating reactions, because some of these dyes when applied undiluted as plain powders are to a certain degree primary irritants.

MICROPAPULAR TUBERCULID AND ROSACEA

A Clinical and Histologic Comparison

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AND
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THIS study was prompted by the belief that resistant rosacea in many cases has been diagnosed cutaneous tuberculosis because of the term "rosacea-like tuberculid" Lewandowsky's¹ classic description, which was reintroduced by MacKee and Sulzberger² and Wile and Grauer,³ will not be repeated in detail here. The eruption occurs on the face and consists of purplish or brownish red papules or papulopustules. There may be distinct hyperemia and telangiectasia of varying amount. Under diascopic pressure a small amount of yellowish brown staining remains. We believe that many cases in which the diagnosis was "rosacea-like tuberculid" may after careful analysis prove to be rosacea and not tuberculosis or, in other instances, the disease may be some other type of tuberculosis, such as lupus miliaris disseminatus faciei, papulonecrotic tuberculid or even papular sarcoid. In many cases the diagnosis of "rosacea-like tuberculid" has been made without strict adherence to the criteria for that diagnosis. Of more importance, in our opinion, the commonly accepted clinical and histologic criteria for the diagnosis of "rosacea-like tuberculid" are often too inconclusive to make a differentiation between that disease and rosacea.

Although in this paper we shall deal chiefly with the histologic observations, we should like to mention briefly other criteria which are used in making a diagnosis of "rosacea-like tuberculid."

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 23, 1948

From the Division of Dermatology, University of Minnesota, H E Michelson, M D, Director, and the Department of Dermatology, Minneapolis General Hospital, Carl W Laymon, M D, Director

1 Lewandowsky, F. Ueber rosacea-ähnliche tuberkulide des Gesichtes, *Cor-Bis für schweiz Aerzte* **47** 1280, 1917

2 MacKee, G M, and Sulzberger, M B. Rosacea-Like Tuberculid of Lewandowsky, *Arch Dermat & Syph* **31** 159 (Feb) 1935

3 Wile, U J, and Grauer, F H. Rosacea-Like Tuberculosis, *Arch Dermat & Syph* **31** 174 (Feb) 1935

CRITERIA OTHER THAN HISTOLOGIC

A Clinical Features of the Eruption Brownish red or purplish papules or papulopustules may be found either in rosacea or the "rosacea-like tuberculid." Many times in rosacea we have found papular lesions which gave positive reactions in diascopic examination, consequently, this feature alone is not of definite differential value. We also have encountered several patients in whom a diagnosis of "rosacea-like tuberculid" was made on the basis of clinical features alone, and yet the histologic examinations showed no tuberculoid structure. In addition, the tuberculin reactions were negative, there was no evidence of tuberculosis elsewhere in the body and the course of the disease and its response to treatment were about those of rosacea. In contrast, we have had patients whose eruptions were diagnosed rosacea, yet the histologic picture showed tuberculoid structure, not of the foreign body type, but with definite tubercle formation.

B Tuberculin Reactions Many observers have stated that patients having the "rosacea-like tuberculid" possess a high sensitivity to tuberculin. This may be true, but there is no doubt that many persons having rosacea also possess a hypersensitivity to tuberculin, so that this criterion is of little value in making a differentiation between the two disorders.

C Concomitant Observations of Tuberculosis Elsewhere in the Body There is no question that the observation of an internal tuberculous focus is important if a patient presents an eruption on the face compatible with a diagnosis of "rosacea-like tuberculid." On the other hand, many patients with rosacea have old healed tuberculous infections. We recently examined a patient who had an eruption on the face which we diagnosed rosacea. Even though there had been intimate association for two years with a partner who had active pulmonary tuberculosis, there were no demonstrable signs of tuberculosis, although the reaction to the Mantoux test was strongly positive. An open source of infection should not sway one in making the differentiation between the micropapular tuberculid and rosacea.

D Course It has been stated repeatedly that the course of the "rosacea-like tuberculid" is protracted. This criterion is not a good basis for differentiation between rosacea and "rosacea-like tuberculid," because there are patients with the latter whose eruption completely disappeared within a few months. On the other hand, certain cases of rosacea prove extremely resistant to all types of therapy and persist for months or years.

E Response to Therapy It has been claimed that because a rosacea-like eruption responds favorably to treatment with arsenic or gold compounds the disorder in question is more apt to be tubercu-

lous On the basis of our experience we cannot verify this concept It has seemed to us that eruptions diagnosed as "rosacea-like tuberculid" have persisted for several months and were little influenced by treatment regardless of type We do not believe that a quick response to treatment with sulfur lotions, roentgen rays or ultraviolet radiation favors a diagnosis of rosacea over "rosacea-like tuberculid" It is true that some cases of rosacea respond to such treatment readily, but many prove as resistant as cases of "rosacea-like tuberculid"

OBSERVATIONS IN THE LITERATURE

In 1940 Laymon and Michelson⁴ commented on a small papular type of tuberculosis of the face Some of the cases presented features which undoubtedly were consistent with a diagnosis of "rosacea-like tuberculid" Others had lesions which remained simply papular and presented no resemblance whatsoever to rosacea Pautrier⁵ and his associates had previously described this form of tuberculosis as the micronodular tuberculid Laymon and Michelson preferred the term micropapular to micronodular, since in the American literature papule is synonymous with nodule as used on the continent Pautrier and Lanzenberg presented their first case in 1937, and other cases were observed subsequently The patients suddenly had an eruption on the face, consisting of small round raised brownish violet papules which were distributed on the forehead, nose, cheeks and chin In 1 case there were lesions on the neck and chest and in another on the ears The individual lesions were sharply circumscribed and showed a yellowish brown stain on application of diascopic pressure Necrosis and ulceration were entirely absent In all of the 4 cases described by Pautrier the cutaneous reactions to tuberculin in dilutions of 1 1,000 were positive No active focus of internal tuberculosis was discovered in any, although 1 patient presented roentgenographic signs of old healed pulmonary tuberculosis

Histologically Pautrier's cases were characterized by an infiltrate which was tuberculoid in structure, located especially about the follicles Pautrier stated the belief that the histologic character of the micropapular tuberculid could be alined closely with that of the papulo-

4 Laymon, C W, and Michelson, H E The Micropapular Tuberculid, *Arch Dermat & Syph* **42** 625 (Oct) 1940

5 (a) Pautrier, L M, and Lanzenberg Tuberculides de la face, a petits nodules non ulcères (acnitis), *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 2159 (Dec) 1937 (b) Pautrier, L M, and Woringer, F Tuberculides micronodulaires de la face, *ibid* **45** 121 (Feb) 1938 (c) Pautrier, L M Tuberculides micronodulaires de la face, *ibid* **45** 700 (May) 1938 (d) Pautrier, L M, and Woringer, F Tuberculides micronodulaires de la face, du cou et de la poitrine, *ibid* **46** 413 (April) 1939

necrotic tuberculid, although there were also rather intimate resemblances to lupus miliaris disseminatus faciei. Pautrier and his colleagues expressed the opinion that it is difficult to separate these tuberculoderms on a purely histologic basis.

Laymon and Michelson expressed the opinion that the eruptions in their patients were identical to those reported by Pautrier and his associates. The lesions differed from those of acnitis in that they were smaller, more numerous, not elevated and without macroscopic central necrosis. After disappearance of the lesions, varioliform scars often resulted. In some cases the eruptions consisted entirely of these small papules, while in others there were papules and some hyperemia which somewhat suggested rosacea. The reactions to tuberculin (Mantoux 1:1,000) were positive in 12 of the 14 cases. It was extremely difficult to differentiate between micropapular tuberculid and sarcoid on the basis of either the clinical or the histologic observations. It seems in retrospect, that the disease in the 2 cases in which there were negative reactions to tuberculin was cutaneous sarcoid.

In 1943 Miescher⁶ published an article on rosacea and the rosacea-like tuberculid. He divided rosacea into three characteristic and more or less well demarcated forms: (1) the pure erythematous telangiectatic form, (2) the glandular hyperplastic form which leads to rhinophyma and is seen almost exclusively in men and (3) the micronodular form which is associated with acne-like papules. He mentioned that this type, in contrast to the former, occurs almost exclusively in middle-aged or younger women. In his study Miescher examined histologically 58 cases of papular rosacea in which there were negative reactions to diascopic pressure. He divided the histologic pictures into three main types and one nonclassifiable type which he called "resorption granuloma." In the first type the infiltrate was entirely banal, in the second there were occasional foci of epithelioid cells (transitional type), and in the third the infiltrate had features indistinguishable from classic cutaneous tuberculosis. In the 59 cases Miescher found 7 of type 1, 9 of type 2 and 37 of type 3, and 5 were nonclassifiable. Miescher stated that the histologic observations in type 3 could not be differentiated from any variety of tuberculosis of the skin. General physical examinations were made in almost all of the cases, but only occasionally were there any concomitant evidences of tuberculosis. In 4 instances there was calcification in the lungs, in 1 pleurisy with erythema induratum and in 3 enlargement of lymph nodes. Miescher

⁶ Miescher, G. Rosacea und Rosacea-ähnliche Tuberkulide, *Dermatologica* 88:150 (July) 1943.

stated the belief that the histologic picture was the most important diagnostic criterion and that the disease in all cases of papular rosacea was a mild form of tuberculid

HISTOLOGIC STUDIES OF THE MICROPAPULAR TUBERCULID

Laymon and Michelson examined many sections from 14 patients whose disease had been diagnosed most carefully as micropapular tuberculid. In all of the cases in which there was any confusion



Fig 1—Micropapular tuberculid. Tuberculoid structure in the upper portion of the cutis. The epidermis remains intact.

concerning another form of tuberculosis the sections were excluded from the analysis. It was found that a pathognomonic picture was lacking and that, even though the clinical diagnosis seemed certain beyond a shadow of a doubt, the histologic picture could never be anticipated. From a survey of the sections the chief impression gained was that the micropapular tuberculid could best be aligned histologically with the chronic indurative tuberculoderms. In analysis of the component parts of the skin from these patients it was found that the epidermis was almost invariably atrophic, which is in keeping with the observations in cases of lupus miliaris disseminatus faciei and sarcoid but in distinct contrast to those associated with lupus vulgaris with which acanthosis is often noted. The epidermis also remained intact, which is in contradistinction to the papulonecrotic tuberculid

In this study we reexamined these sections plus additional ones from more recent cases. The infiltrate was variable. In some it was high in the corium and consisted of whorls of pure epithelioid cells with an occasional giant cell and no coexisting acute inflammation. In others it appeared as vertically placed lobes extending down to the hypoderm, and in others there was tuberculoid structure surrounded by considerable banal inflammation. Necrosis and liquefaction were not encountered.

There was undoubtedly a strong resemblance between the histologic pictures of the micropapular tuberculid and sarcoid. It was most difficult to draw sharp lines of differentiation between the micropapular tuberculid, cutaneous sarcoid and lupus miliaris disseminatus faciei, and it seemed certain that histologic examination alone was inadequate for differentiation of these disorders.

In order to evaluate the histologic observations associated with the micropapular tuberculid, Laymon and Michelson performed biopsies of 30 patients with rosacea. After examination of sections from these patients, it was believed that there should be no confusion microscopically between true rosacea and the tuberculids of the face. Laymon and Michelson expressed the opinion that in those sections in which giant cells were observed they were usually located about a degenerated follicle and that true tubercle formation or even collections of epithelioid cells were absent. Continued observation over a period of eight years, however, has caused us to alter our views on this subject. After observing patients whose eruptions were diagnosed "rosacea-like tuberculid" clinically and in whom absolutely no evidence for a diagnosis of tuberculosis could be found, and after observing patients whose eruptions were diagnosed rosacea and who presented tuberculoid structure histologically, we decided to continue the study. During the past few years at various meetings we have observed facial eruptions diagnosed as "rosacea-like tuberculid" in cases in which we felt that the evidence was insufficient to make such a diagnosis. Thus we have gained the impression that true "rosacea-like tuberculid" is much rarer than is popularly believed.

HISTOLOGIC STUDIES OF ROSACEA

In this study biopsies were performed in 78 cases in which we clinically considered the disease as incontestable rosacea. The histologic pictures were divided into three types: (1) those in which the infiltrate was purely banal, (2) those characterized by a few foci of tuberculoid structure, consisting of sparse epithelioid cells with or without one



Fig 2—Rosacea Banal infiltrate distributed diffusely throughout the cuts
The infiltrate is predominantly lymphocytic



Fig 3—Rosacea Banal infiltrate located around the follicle

or more giant cells (Miescher's transitional type), and (3) those in which there was classic tuberculoid structure, even with tubercle formation

In some sections in which the disease was classified as type 1 the infiltrate was deposited rather diffusely throughout the corium, whereas in others it was arranged in foci especially about the follicles and sebaceous glands. The degree of intensity of the infiltrate varied considerably, being rather sparse in some sections and extremely heavy in others. In some sections the cellular infiltrate was almost purely lymphocytic, while in others there were large numbers of polymorphonuclear leukocytes. In most sections the vessels of both the deep



Fig 4—Rosacea Banal infiltrate in the form of a pustule

and superficial layers of the cutis were dilated. Perivascular infiltration was common. In some there was definite hypertrophy of the sebaceous glands with the formation of new glands and fibrous connective tissue. Plasma cells were seen in many sections and eosinophils in a few. In several sections there was edema of varying degree of both the epidermis and the cutis. Sixty-seven of the 78 cases which we examined were placed in this category.

Nine of the 78 cases showed tuberculoid structure of slight degree as small foci of epithelioid cells with or without one or more giant cells interspersed among the foci of nonspecific infiltrate. Areas of tuberculoid structure were seen both in the perifollicular and inter-



Fig 5—Rosacea Ruptured follicle surrounded by tuberculoid structure of foreign body type



Fig 6—Rosacea Mixture of banal infiltrate and tuberculoid structure

follicular regions. In only 2 of the 9 cases were there ruptured follicles which might conceivably produce a foreign body type of reaction, in all other cases the follicles seemed entirely normal.

In 2 cases in which the disease clinically was rosacea, classic tuberculoid structure was observed. In both were small sharply defined cellular infiltrations in the upper and middle portions of the cutis consisting of nests of epithelioid cells with a centrally placed giant cell of the Langhans type and a peripheral zone of lymphocytes. No central necrosis was seen in either of the cases. There was character-



Fig 7—Rosacea. Diffuse distribution of banal infiltrate.

istic tubercle formation in both. It is noteworthy that in 1 of these cases two biopsies were performed of similar papular lesions on different parts of the face. Sections of one of the lesions showed characteristic tuberculoid structure with tubercle formation, while those from the second lesion showed an entirely nonspecific infiltrate. In the future we hope to perform two or more biopsies on various parts of the face of patients with rosacea in order to determine how frequently some lesions show tuberculoid structure while others in the same patient show only banal inflammation.



Fig 8—Rosacea The section is from the same patient as the section illustrated in figure 7 The biopsy was performed from another lesion and shows tuberculoid indistinguishable from that occurring in micropapular tuberculoid



Fig 9—Rosacea Tubercle formation in the middle part of the cutis

COMMENT

The histologic observations in our cases of papular rosacea do not coincide with those of Miescher, inasmuch as he found that the great majority of his patients showed tuberculoid structure (approximately 80 per cent). In contrast only 14 per cent of our patients presented such changes. Thus Miescher found tuberculoid structure six times as frequently as we. The observations in our study do not permit us to draw the same conclusions as Miescher, who stated the belief that all patients with rosacea represented a mild type of tuberculid. We definitely feel, however, that in some cases of rosacea there is a histologic picture which may be confused with that of certain tuberculoderms, and occasionally the tuberculoid structure attains such a perfect stage of development that even the trained eye cannot differentiate it from that of true cutaneous tuberculosis. There is no constant histologic means of differentiation between rosacea and the "rosacea-like tuberculid." Without a doubt, biopsies have been performed in many cases of rosacea and a diagnosis of cutaneous tuberculosis has been made merely because of the presence of a few epithelioid cells and/or giant cells.

The main object of this paper is to caution against the diagnosis of "rosacea-like tuberculid" without careful and prolonged studies. The psychic trauma which attends a diagnosis of tuberculosis should be avoided whenever possible. We should like to point out again that with all the present means at our disposal it is occasionally impossible to make a definite differentiation between rosacea and "rosacea-like tuberculid."

SUMMARY

Biopsies in 78 cases of rosacea were performed and the results compared with those in 14 cases of micropapular tuberculid.

Well developed tuberculoid structure can occur in rosacea. In approximately 86 per cent of our cases there was banal inflammation, and in 11 per cent there were a few sparse foci of epithelioid cells. In 2 cases (3 per cent), however, in which there were clinical features of rosacea and not tuberculid, characteristic tubercle formation was observed. In 1 of the latter group two biopsies were performed, one showed characteristic tuberculoid structure and the other only banal inflammation.

The disease in many cases of resistant rosacea has been diagnosed as tuberculosis because of the term "rosacea-like tuberculid." We believe that micropapular tuberculid is a preferable and more precise name. The commonly accepted clinical and histologic criteria for the diagnosis of "rosacea-like tuberculid" are often too inconclusive to permit us to make a differentiation between that disease and rosacea.

The diagnosis of micropapular tuberculid should be reserved for those cases in which the disease can so be diagnosed without reservation and which possess the necessary criteria for that diagnosis the individual lesion should resemble a minute lupus nodule, there should be some concomitant evidence of tuberculosis (positive tuberculin reaction, roentgenologic signs, etc), and the histologic features should be frankly tuberculoid In cases in which there are pustules and telangiectasia in addition to lupoid papules, the diagnosis of tuberculid should be made with extreme caution The micropapular tuberculid is much rarer than commonly believed

ABSTRACT OF DISCUSSION

DR MARCUS R CARO, Chicago The authors are to be congratulated on their courage in performing facial biopsies in 78 patients with rosacea At first glance it would seem that a comparatively minor disease does not warrant such intensive histologic investigation The importance of the work may be gaged, however, by the necessity of our finding some method for differentiating clearly between rosacea and a mimicking disease that is tuberculous in nature I agree with the conclusions that on histologic grounds alone one cannot always make such a distinction Many patients with rosacea have been given a diagnosis of tuberculosis, with all the emotional and social implications of such a diagnosis, merely because a biopsy demonstrated a few epithelioid cells or giant cells Patients and physicians alike are often so completely overawed by the finality of a laboratory report that it is the duty of the histopathologist to withhold the diagnosis of rosacea-like tuberculid in these cases unless the histologic picture is definitely tuberculoid I agree with the authors that all of their criteria should be met before one labels a disease as tuberculous, that is, resemblance to a minute lupus lesion, concomitant evidence of tuberculosis and the histologic features of tuberculosis In addition, I should like to require a negative reaction to a therapeutic test for rosacea It has been my practice to treat as possibly having rosacea all patients who seem to have rosacea-like tuberculid It has been gratifying to see several patients, for whom the tuberculosis diagnosis had been generally accepted, respond well to treatment with 40 per cent sulfur paste and roentgen rays or cryotherapy along with the general treatment for rosacea With the rigid application of these criteria and the therapeutic test I feel certain that the diagnosis of rosacea-like tuberculid will become extremely rare Finally, I should like to make a plea for the retention of rosacea-like tuberculid as the appellation for this dermatosis It carries the advantage of established usage, and it calls to mind at once the causative nature, the location on the face and the approximate clinical appearance of the disease A label that can perform all these functions is worth keeping

DR MARION B SULZBERGER, New York Dr Laymon and Dr Schoch's presentation is very interesting, stimulating, and accurate, and I am in hearty agreement with their conclusions These conclusions do not differ radically from those which MacKee and I presented in our first American article on this subject (ARCH DERMAT & SYPH 31 159 [Feb] 1935) We too stressed the great difficulties of differential diagnosis and the fact that the histologic picture was by no means a pathognomonic criterion for distinction between acne rosacea and rosacea-like tuberculid Since our published report in 1935, despite the fact that we have seen hundreds of cases of classic rosacea and many cases of facial

tuberculoderms, including lupus miliaris disseminatus faciei, in all of our large material at the New York Skin and Cancer Unit and in private practice, I have found only a dozen or so cases which I felt reasonably certain were of rosacea-like tuberculid. This low incidence in fifteen years suggests that truly typical rosacea-like tuberculid is rare. Though there were so few cases in which we felt certain of the diagnosis, there were many in which the differential diagnosis remained uncertain, even at the end of all our investigations.

I would like to add another dermatosis to the differential diagnosis mentioned by Dr. Laymon and Dr. Schoch, and that is micropapular iododerma or bromoderma of the face. Some of those conditions can take on an appearance closely simulating acne rosacea and some suggest rosacea-like tuberculid. Dr. R. L. Baer and I have favored strongly the tentative diagnosis of rosacea-like tuberculid in several cases in which the disease was eventually shown to be iododerma or bromoderma and which cleared up only after elimination of exposure to the responsible drugs and recurred when the drugs were again administered. In addition to the procedures mentioned by Dr. Laymon, in all our attempts at differential diagnosis at the New York Skin and Cancer Unit we regularly employ the quantitative tuberculin tests and often bacteriologic examinations and sedimentation rate determinations. I would like to emphasize that the regular use of quantitative tuberculin testing brings out one important point which Dr. Laymon mentioned and, I believe, Dr. Michelson also alluded to this morning: the condition in these cases resembles lupus miliaris disseminatus faciei and sarcoids, on the one hand, and papulonecrotic tuberculids, on the other. Many rosacea-like tuberculids are therefore likely to be either relatively anergic (hypoergic) to tuberculin, like the sarcoid group, or at the opposite end of the scale and strongly hypersensitive to tuberculin, like some papulonecrotic tuberculids.

DR. STEPHEN ROTHMAN, Chicago: I would like to make a few remarks, not so much about the differential diagnosis of rosacea and rosacea-like tuberculid but rather about the concept of rosacea-like tuberculid itself. Histologically tuberculoid structure of lesions is not enough to make a disease a "tuberculid." The diagnosis of a true tuberculid requires the presence of a tuberculous focus and a high degree of tuberculin sensitivity. Dr. Robert H. Snapp of the Dermatology Department of the University of Chicago School of Medicine reviewed 20 cases which, clinically and histologically, all would have agreed were typical cases of rosacea-like tuberculid. Of these 20 patients, only 1 had active tuberculous focus and another one had a tuberculin sensitivity to a dilution higher than 1:10,000. Thus, I feel that there is no evidence whatsoever that Lewandowsky's disease has anything to do with the tubercle bacillus. Bacilli have never been shown to be present in these lesions. The situation is somewhat similar to lupus miliaris disseminatus faciei, the tuberculoid structure of which caused some persons to believe it to be of tuberculous origin.

Dr. Snapp's review furthermore showed that patients with rosacea-like tuberculid recover spontaneously. All patients completely recovered after one to four years with or without therapy. Four of them had a relapse after several years of complete freedom of signs and symptoms. These relapses also cleared up in an average of one and a half years. True rosacea never behaves this way. The primary question is not whether Lewandowsky's disease is a rosacea-like tuberculid or a micropapular tuberculid but whether it is a tuberculid at all.

DR. CARL W. LAYMON, Minneapolis: It seems that we all agree concerning most points. I am not quite ready to go so far as to deny that there is such an entity as micropapular tuberculid, but I believe that the diagnosis is made too frequently. Many times our group has discussed the point which Dr. Rothman

just mentioned I agree with Dr Caro that some cases of rosacea certainly respond to various measures, but I think that there are enough cases of rosacea which are resistant to treatment to make that criterion not infallible as far as the differential diagnosis between rosacea and micropapular tuberculid is concerned

I think that Dr Sulzberger brought out a good point Many times we have been uncertain as to whether a certain case was one of so-called rosacea-like tuberculid and even after observing the patient for weeks or months we were unable to make a definite diagnostic decision Dr Rothman's point about the difficulty of finding evidence of internal tuberculosis in this particular tuberculid is true But, as Dr Michelson pointed out earlier, it is extremely difficult in many other forms of tuberculosis to find concomitant evidence of tuberculosis

There was insufficient time to bring out the criteria which I consider the most important in the diagnosis of the micropapular tuberculid The individual lesion should resemble a minute lupus nodule There should be intense search for concomitant evidences of tuberculosis elsewhere in the body, including positive reaction to tuberculin tests, roentgenologic signs or other observations, and the histologic features should be frankly tuberculoid Again I should like to caution against hasty diagnosis in cases in which there are pustules and telangiectasia in addition to lupoid papules In those cases, a diagnosis of micropapular tuberculid should be made with extreme caution

EXOGENOUS CUTANEOUS LEISHMANIASIS PROVED BY CULTURE

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REPORTS of a disease simulating the type of lesion seen in cutaneous leishmaniasis were first made in 1756 by Hasselquist and Russel¹ Also in the middle of the nineteenth century, the same type of lesion was described by French medical officers in Africa Laveran² demonstrated in 1880 that this condition could be transmitted and that a fly was an important factor In 1885 Cunningham described the histologic picture and stated that there were bodies within the cells which were circular to elliptic in shape Ryan, in 1886, also described some cells which were filled with bodies which he regarded as cocci with capsules He attempted cultures in human blood but obtained no results It was not until 1903 that Leishman and Donovan made independent reports describing the protozoan During the same year Wright³ in Boston described the organisms found in the first case of cutaneous leishmaniasis reported in this country Since then there have been approximately 30 cases reported in the United States, all of which have been exogenous In only 1 instance has the disease in cases reported in this country been proved by actual culture of the flagellate from the lesion Packchamian⁴ in 1945 reported 2 cases in which the disease was actually proved by culture, both cases were of exogenous, and were of American soldiers who had returned to United States from the Near East

REPORT OF A CASE

M K, a man 26 years of age, left his home in New York City, traveled to Beirut, to Marseilles, France, and returned to New York from New York directly to Austin, Texas, where he was in good health then In February, 1945, he was in good health then

From the Section on Dermatology, University of Texas Medical Branch, Austin, Texas

1 Hasselquist and Russel, *Experiments, London, 1756*

2 Laveran, C L, *Leishmaniose americaine, Paris, 1880*

3 Wright, J, *Experiments, Boston, 1903*

4 Packchamian, *Experiments, 1945*

on the dorsum of the left hand, but he thought that it was an injury and did nothing about it. It gradually increased in size, and in March 1947 he noticed a small similar area about 2 cm below the lobe of the left ear. Both areas increased in size until they were elevated about 0.5 cm above the surface of the skin and were about 2.5 cm in diameter. In May 1947 he consulted the University of Texas Health Service. At that time he presented on the dorsum of the left hand (fig 1), about 3 cm proximal to the fourth metacarpal phalangeal joint, an area about 2.5 cm in diameter, elevated about 0.5 cm, which was dusky red with indurated borders and with a central ulceration which was covered by a crust. There was a similar lesion 2 cm below the left ear lobe, but it was not ulcerated at this time. A smear was taken from the ulcerated area on the hand. On the smear stained with Wright's stain Leishman-Donovan bodies (fig 2) were seen, the slides were sent to Dr A. Packchaman of the Department of Bacteriology of the University of Texas Medical School, Galveston, Texas, for confirmation. Under the supervision of Dr Packchaman I obtained material for culture by the following pro-

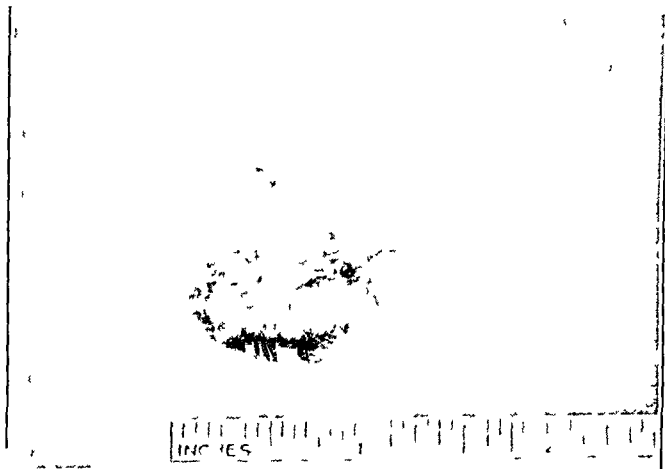


Fig 1—The lesion as it was first seen in May 1947

cedures. The area was painted with tincture of iodine and after anesthetization with 1 per cent procaine hydrochloride, 0.2 cc, in isotonic sodium chloride solution was injected into the indurated border of the lesion, the material was removed by gentle aspiration. This material was placed on NN mediums as described by Dostrovsky and Sagher.⁵

The patient was rather insistent that the lesions be surgically excised, and after a review of the previously reported cases it was decided that this was probably the treatment of choice. Both lesions were surgically excised in July 1947 including about 1 cm of normal skin surrounding the lesions, and the wounds healed without difficulty. By this time the culture had grown and flagellar forms (fig 3) were seen and demonstrated on a smear made from the culture from the original lesion. On Feb 23, 1948, six months after surgical excision, the patient returned with a small nodule about 1 cm proximal to the scar on the dorsum of the left hand, this nodule had appeared about three weeks earlier. Some material was removed from the lesion by the use of a sterile syringe and needle and with the procedure described previously in this paper. Smears were made, and Leishman-

5 Dostrovsky, A., and Sagher, F. Diagnostic Significance of Culture Method in Cutaneous Leishmaniasis, *Arch Dermat & Syph* 54: 542-551 (Nov) 1946

Donovan bodies were demonstrated. Nothing was done to this lesion, and it gradually decreased in size until in June, when it was last observed, there was no longer a papule but a depressed atrophic scar just proximal to the scar from the original excision.

COMMENT

The rarity of cutaneous leishmaniasis in this country indicates that many physicians have not had an opportunity to observe a case. Therefore, a brief discussion of the clinical picture will be presented. The

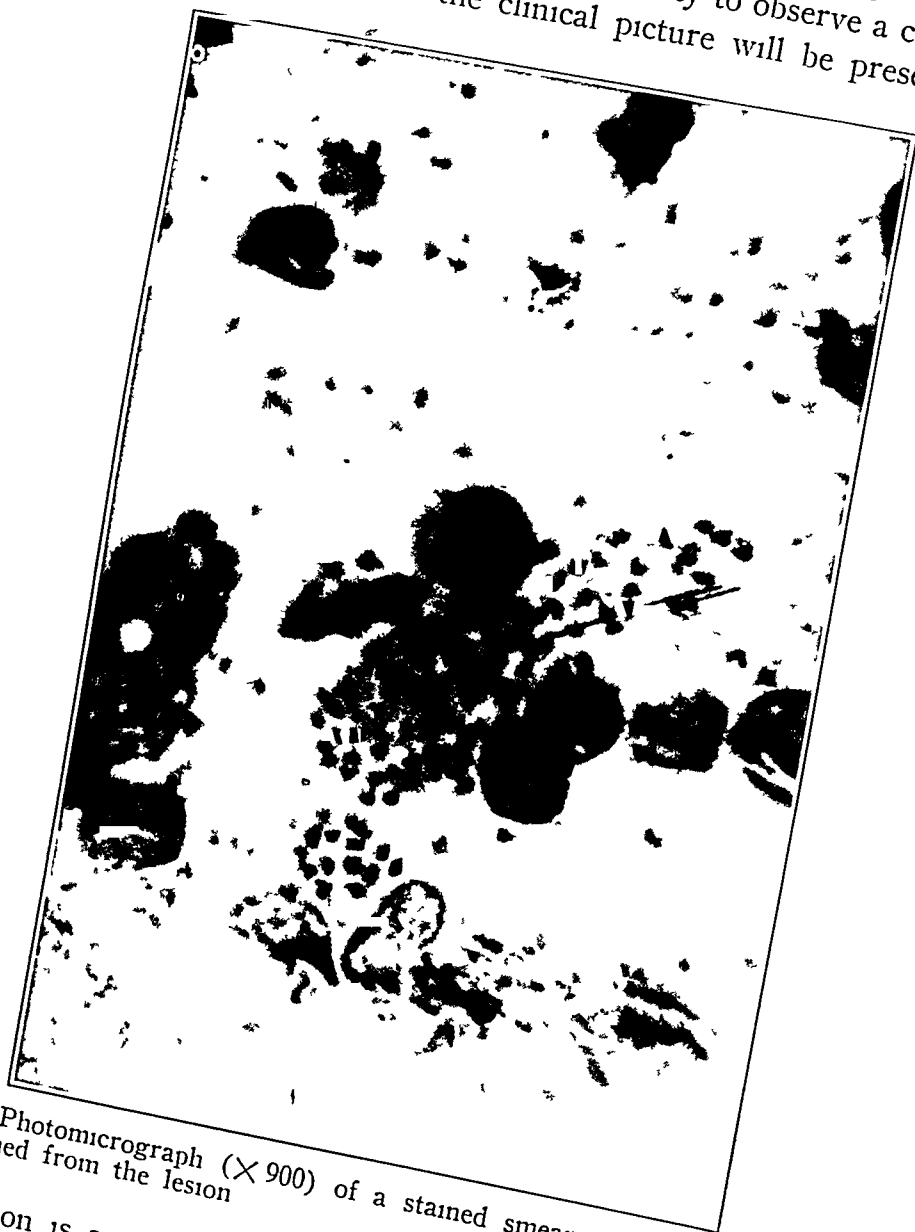


Fig. 2—Photomicrograph ($\times 900$) of a stained smear of Leishman-Donovan bodies obtained from the lesion.

original lesion is a red papule which usually appears on the exposed surfaces of the body and which gradually increase in size and thickness. The lesion then usually ulcerates in the center and becomes covered with a thick crust. Puente and Ambrosetti,⁶ in their description of the clinical picture of cutaneous leishmaniasis, state that the lesion is usually

⁶ Puente J. J., and Ambrosetti, F. A. Leishmaniasis cutánea tipo botón de Oriente, *Rev argent dermatosis* 24 403-415, 1940

cal appearance of the lesion, described a grayish brown squamous crust studded with numerous conical projections on its lower aspect, with a pinkish yellow translucent appearance to the infiltrated area. They also point out that there is usually no lymph node reaction and no fever, but stated that fever and chills may appear. They emphasized that there is little to compare between cutaneous leishmaniasis and American leishmaniasis. As described by Fox,⁷ American leishmaniasis has a tendency to extend involve the mucosa of the nose and throat,



Fig 3—Photomicrograph ($\times 900$) of a stained smear of flagellar forms obtained from culture of the lesion

show little tendency to heal and lead to cachexia and death. Cutaneous leishmaniasis has none of these features, and it tends to heal spontaneously in twelve to eighteen months.

It is apparently uncertain whether oral or nasal infections in the Sudan are associated with a special type of parasite. Unless Kirk⁸

7 Fox, H. American Leishmaniasis. Report of Cases Observed in Brazil, *Arch Dermat & Syph* **23** 480-502 (March) 1931

8 Kirk, R. Leishmaniasis in the Anglo-Egyptian Sudan. Cutaneous and Mucocutaneous Leishmaniasis, *Tr Roy Soc Trop Med & Hyg* **35** 257-270 (March) 1942

encountered a remarkable series of double infections, his observations certainly suggest that the parasites of Sudan kala-azar may at times produce cutaneous and oral-nasal infections, although this has not been found true elsewhere. One of the more unusual manifestations was described by Angevine and his co-workers⁹. They described 2 cases of leishmaniasis in which the primary and most important symptom was enlargement of the cervical lymph nodes. The disease in these cases was diagnosed by biopsy of the lymph nodes. *Leishmania* were demonstrated in the tissue in both cases, and organisms were grown in the culture from 1. This is unusual, because the ordinary lesions give no constitutional symptoms and no regional adenopathy. The pathologic picture was that of atrophy and disappearance of the epidermis, a lymphocytic filtrate with many large cells containing large numbers of the Leishman-Donovan bodies.

Berberian¹⁰ and many others have emphasized the long incubation period. In 3 cases reported by Berberian the incubation periods were eighteen, thirty and fifty-six months, respectively. Dwork,¹¹ Gelber,¹² Silverberg and Henschel¹³ and Templeton¹⁴ also emphasized the possibility of a long incubation period. Berberian¹⁵ conducted extensive studies on the time required for the development of immunity following vaccination and after natural infection. He demonstrated that the immunity is produced slowly and can be considered complete only when the *Leishmania tropica* can no longer be found in smears from the sore. He concluded that the immunity is dependent on the appearance of the sore and cannot be considered complete until the processes of healing are apparent. This is demonstrated in the case presented here. Two lesions were surgically excised, and six months after surgical excision another active lesion developed. At the time of surgical excision, six months after the appearance of the sore, organisms were still present and

9 Angevine, D M, Hamilton, T R, Wallace F G, and Hazard, J B. Lymph Nodes in Leishmaniasis. Report on Two Cases, *Am J M Sc* **210** 33-38 (July) 1945

10 Berberian, D A. Cutaneous Leishmaniasis, *Arch Dermat & Syph* **49** 433-435 (June) 1944

11 Dwork, K G. Cutaneous Leishmaniasis (Oriental Sore) in the United States and Canada. Survey of Literature and Report of Four Cases, *Arch Dermat & Syph* **45** 676-684 (April) 1942

12 Gelber, A. Oriental Sore Possibly Contracted in the United States, *Arch Dermat & Syph* **46** 739-740 (Nov) 1942

13 Silverberg, M G, and Henschel, E J. Oriental Sore in the United States, *Arch Dermat & Syph* **46** 705-710 (Nov) 1942

14 Templeton, H J. Cutaneous Leishmaniasis Experimentally Produced, *California & West Med* **54** 70-71 (Feb) 1941

15 Berberian, D A. Cutaneous Leishmaniasis (Oriental Sore). Vaccination Against Oriental Sore with Suspensions of Killed *Leishmania Tropica*, *Arch Dermat & Syph* **50** 231-236 (Oct) 1944

were demonstrable histologically and proved by culture. Sagher,¹⁶ using *L. tropica* vaccine, demonstrated that the scar of leishmaniasis will give a negative reaction when the vaccine is injected into the scar only if the immunity is complete and positive if there are still living organisms present. Therefore, in my case the reaction to the test would probably have been positive before the development of the last papule. He also stated that in 10 per cent of the cases there is recurrence at the periphery of the scar months or years following apparent healing. Thus, it would seem that this test would be of considerable value in differentiating actual cure from apparent cure. Since the patients might serve as a source of infection, it seems that this would be a good procedure to follow in presumably healed patients.

Mogath¹⁷ stated that the flies which carry this disease are not present in the United States. If this were true, of course, there would be no possibility of the disease becoming prevalent in this country. However, Packchamian in 1946¹⁸ stated that six species of sand flies, genus *Phlebotomus*, are present in the United States, and their distribution is given. At least one of the species is found in each of the following states: Texas, Alabama, Georgia, North Carolina, Maryland, Virginia and Louisiana. Since these sand flies are present within the United States, Packchamian pointed out that indigenous species of *Phlebotomus* may some day become infected from these patients and thus establish leishmaniasis in the United States, with dogs perhaps becoming a reservoir of infection.

The fact that many American soldiers contracted this disease overseas is shown by Ball and Ryan,¹⁹ who reported 499 proved cases of leishmaniasis in American forces in the Middle East. Therefore, there may be other cases which were in the incubation period when the soldiers returned to this country. In addition to the danger from returning soldiers with the disease in an incubation period is the danger from students from the Near East who are seeking education in this country. At the University of Texas there are 28 students from the Near East, 21 of whom had scars which were suggestive of cutaneous

16 Sagher, F. Response of Scars of Cutaneous Leishmaniasis to Injection of *Leishmania Tropica* Vaccine, *Brit J Dermat* **59** 205-213 (June) 1947, *Leishmania Vaccine Test in Leishmaniasis of Skin*, *Arch Dermat & Syph* **55** 658-663 (May) 1947.

17 Mogath, T. B. Consideration of Certain Diseases of International Importance, *M Clin North America* **31** 983-994 (July) 1947.

18 Packchamian, A. The Distribution of Species of Sandflies, Genus *Phlebotomus*, in the United States and Their Relation to the Transmission of Leishmaniasis, *Texas Rep Biol & Med* **4** 35-41, 1946.

19 Ball, D., and Ryan, R. C. Cutaneous Leishmaniasis, *Bull, U S Army M Dept.*, 1944, no 79, pp 65-73.

leishmaniasis The patient reported here is 1 of the 6 who apparently had not had cutaneous leishmaniasis when they entered this country

Packchanian⁴ and Sagher and Dostrovsky⁵ insisted that for an absolute diagnosis of cutaneous leishmaniasis it is essential to culture the flagellar forms of the parasite on suitable mediums Packchanian stated that occasionally yeastlike micro-organisms or other extraneous material are found in smears and are confused with Leishman-Donovan bodies and therefore recommended culture for the absolute diagnosis of cutaneous leishmaniasis Dostrovsky and Sagher⁵ further emphasized the importance of cultures by demonstrating positive cultures in 20 of 29 cases when smears were positive in only 2 of the 29

SUMMARY

The history of this disease is briefly reviewed A case of cutaneous leishmaniasis occurring in a student from Syria now at the University of Texas is presented The clinical picture of the disease is described, and the rarer manifestations are mentioned and discussed The long incubation period, the development of immunity, the possibility of the disease becoming prevalent in the United States and the importance of culture in establishing the diagnosis are discussed

Dr A Packchanian, Professor of Bacteriology, University of Texas Medical School, Galveston, Texas, cooperated in the preparation of this paper

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TUBERCULOSIS CUTIS COLLIQUATIVA (TUBERCULOUS GUMMAS)

Healed Rapidly with Local Applications of Promin® Jelly Report of a Case

JOHN GARB, M D
NEW YORK

THE FOLLOWING report is of a patient with tuberculous ulcerations of the skin which failed to respond to 6 filtered units of roentgen rays in six months but completely healed in seven weeks with topical applications of promin® jelly¹

REPORT OF A CASE

History—K. B.,² a Negress aged 37, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 10, 1945, presenting lesions of seven months' duration. She gave a history of having had "rheumatism of the hip" at 16 years. The first three pregnancies resulted successively in a stillbirth at nine, a miscarriage at six and a premature baby at seven months, which lived for seven months. She was treated for one year for syphilis at the New York Department of Health with injections of bismuth preparations and arsenicals from 1938 to 1939. She received twelve more "hip" injections in 1941 by a private physician, who then discharged her as cured. The reactions to the last six or seven serologic tests were said to be negative. She complained of pains in the chest and shortness of breath on moderate exertion.

Dermatologic Examination—The patient presented 3 ulcerated lesions. They were located on the upper and inner border of the left breast (fig 1), on the base of the left side of the chest and on the middle of the anterior surface of the left arm. They commenced in June, July and October 1944, respectively. The lesion on the breast was irregular, raised a few millimeters, with central ulcerations and with many fine clawlike keloidal branchings extending to the periphery. It was tender and infiltrated, the tissues being matted together, but the whole mass moved rather freely on the subcutaneous structures. The lesion on the chest was horizontally located, 20 by 0.5 cm in size and 10 cm in thickness. It had an oblong central ulceration and sloping rounded surfaces and was doughy in con-

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology (Dr. Marion B. Sulzberger, Director) of the New York University Post-Graduate Medical School.

1 Chemically promin® is sodium p,p'-diaminodiphenylsulfone-N,N' dideutrose sulfonate and is a sulfone derivative the nucleus of which is 4,4' diaminodiphenylsulfone. Promin® jelly contains 5 per cent promin®, 3 per cent tragacanth, 10 per cent propylene glycol and 80 per cent water (Parke, Davis & Company, Detroit).

2 The patient was presented before the New York Dermatological Society, April 24, 1945 (Wise, F. Tuberculosis of the Skin, Arch. Dermat. & Syph. 55:587 [April] 1947) and before the Bronx Dermatological Society, Jan. 15, 1948 (Garb, J. Tuberculosis Colliquativa Treated Successfully Under Promin Jelly).

sistency The lesion on the left arm was 25 by 15 cm in size, ovoid, with an ulceration in the center which was excavated and with a dirty grayish base from which a mucopurulent fluid exuded There was a satellite pea-sized lesion 3 cm below it The general physical examination brought to light no abnormalities

Laboratory Data—The urine was normal The Wassermann and Kahn reactions of the blood were negative The hemogram was normal except for a low leukocyte count of 3,800 Chemical examination of the whole blood on May 1, 1945 revealed 7.5 mg of nonprotein nitrogen (normal 25 to 35 mg) and 1.7 mg of uric acid (normal 2 to 4 mg) per hundred cubic centimeters of blood The ratio of urea nitrogen to nonprotein nitrogen was 32 per cent (normal 35 to 45) The glucose content was normal The ascorbic acid content in the blood plasma was 0.3 mg per hundred cubic centimeters (normal 0.7 to 1.4 mg) Quantitative intra-



Fig 1—Photograph taken Oct 25, 1945, showing large irregular ulceration in the upper part of the inner surface of the left breast

cutaneous tests with old tuberculin (Koch) were performed April 26 in the allergy department These tests elicited a 1 plus reaction in 1 to 1,000,000, 2 plus in 1 to 100,000 and 3 plus in 1 to 10,000 concentration

Roentgenographic examination of the chest on April 25 by Dr William H Meyer revealed "clear peripheral lung fields except for a slightly diminished pulmonary ventilation probably exudative in character"

The material obtained from the ulcerated lesion on the left breast was inoculated into a guinea pig on July 19 The animal was killed on August 25 Smears taken from enlarged lymph nodes examined by Dr Waid J MacNeal were positive for *Mycobacterium tuberculosis*

Histologic Observations—From a section taken from the lesion of the arm the histologic diagnosis, by Dr Charles F Sims, was tuberculosis of the skin (fig 2) The description follows

"The epidermis was decidedly acanthotic in the center of the section. However, at one point it had broken down. The upper, middle and deep parts of the corium presented a massive cellular reaction composed of groups of epithelioid cells surrounded in part by a moderate mantle of small round cells. In the area of ulceration many polymorphonuclear cells could be noted. Some scattered giant cells were visible. The vessels throughout were moderately dilated."

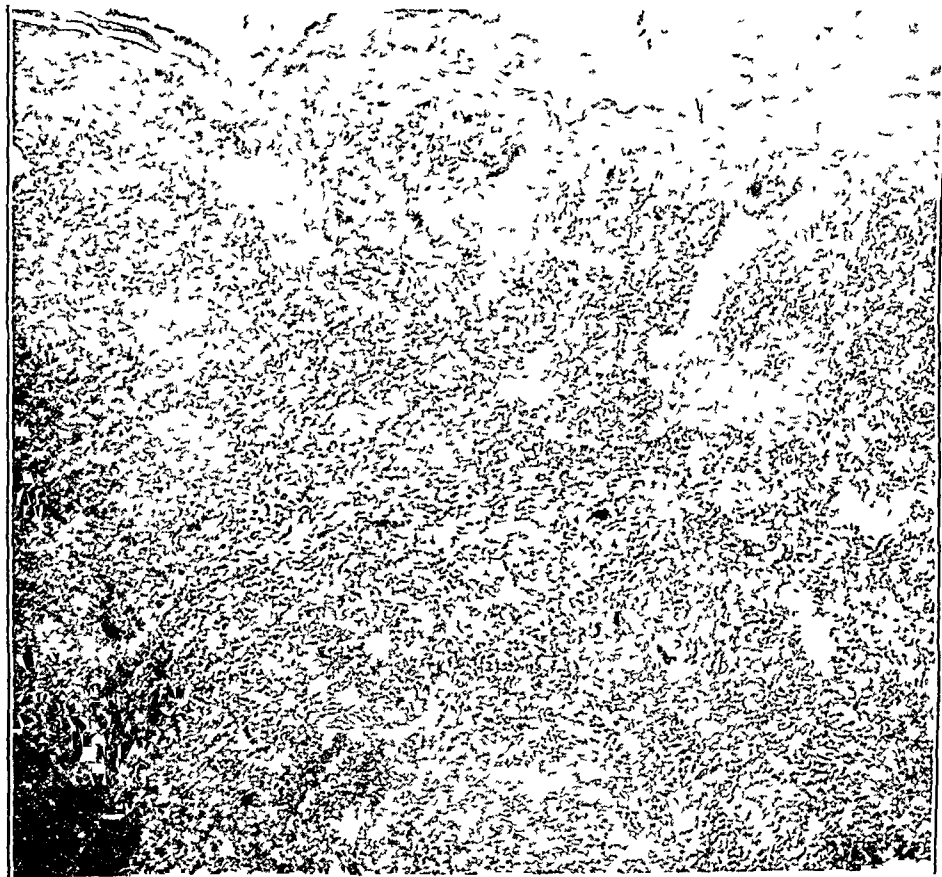


Fig 2—Photograph showing the massive cellular reaction composed of groups of epithelioid cells surrounded in part by a moderate mantle of small round cells. Some polymorphonuclear cells are seen in the area of the ulceration with some scattered giant cells ($\times 178.5$)

Treatment—Between April 26 and October 16, the patient received 6 units of roentgen rays (2,700 r), 1 unit once a month, filtered through 1 mm of aluminum to each of the three lesions. There was no noticeable improvement.

On October 25, 5 per cent promin[®] jelly was prescribed to be applied three times daily to the ulcerating lesions (fig 1). Eight days later the patient stated that she had no more pain in the affected areas. On December 1 the lesions already showed signs of healing, and on December 15 they were entirely healed.

(fig 3) The patient was seen regularly. On April 8, 1948, the patient presented a 10 cm-sized scar in both diameters on the inner and outer quadrant of the left breast. It was irregular, serpiginous, blackish hyperpigmented, thinned and atrophic. It contained areas of depigmentation and had a zone of light brownish pigmentation for about 2.5 cm around it (fig 4). On the base of the left side of the chest was a scar 3.7 cm long. There was a 1.6 cm rounded scar on the anterior surface of the middle of the left arm. There was a half-dollar-sized vaccination scar just above it and a horizontal keloidal growth of 9 cm on the outer surface of the left elbow.

At no time was there a recurrence of the ulcerations, pain, discomfort or any untoward reaction from the promin® jelly applications.



Fig 3—Photograph taken Dec 15, 1945, showing the healed lesion of fig 1.

COMMENT

The histologic section showing typical tuberculous structure, and the positive guinea pig inoculation leave no doubt that the lesions were tuberculous and not syphilitic. The failure of the ulcerations to respond to 6 units of filtered roentgen rays (2,700 r) in six months and the rapid healing under treatment with promin® jelly, with relief of pain in eight days, appear to me to eliminate the possibility that delayed effects of the roentgen rays were a deciding factor in this good result.

Tytler and Lapp³ used 5 per cent promin® in tragacanth jelly by injection into tuberculous glands and abscesses in 10 patients. One healed "spectacularly" and three abscessed cavities closed completely.

³ Tytler, W. H., and Lapp, A. D. Treatment of Superficial Tuberculous Lesions by Local Application of Promin, *Brit. M. J.* 2: 748 (Dec 26) 1942.

in two weeks. They concluded that these results justified a more extensive trial in superficial as well as in deep-seated lesions accessible to injectable material.

Edelston⁴ reported a case of a woman aged 55 who had a tuberculous sinus in the region of the right scapula, which failed to heal with ordinary surgical treatment. Improvement was almost immediately seen when 5 per cent "promanide"⁵ jelly was used. He also expressed the opinion that "promanide" jelly has a definite place in the therapy of tuberculous wounds and sinuses.

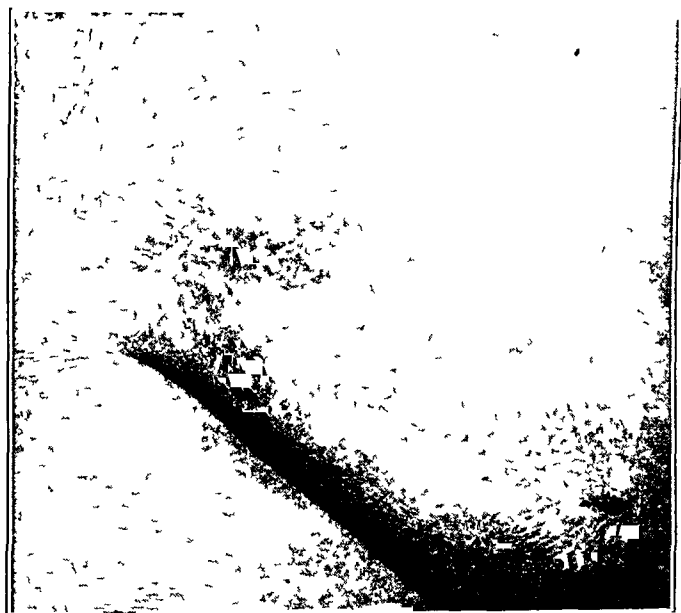


Fig 4—Photograph taken April 8, 1948, showing the terminal stage of the healed lesion of fig 1, with atrophic scarring. The ulcerations on the base of the left side of the chest and on the outer surface of the left elbow showed correspondingly similar results to the ulceration of the left breast.

Hinshaw and Feldman⁶ stated "Promin may also be applied topically to superficial lesions of tuberculosis such as draining sinuses in the thoracic wall, sinuses from tuberculous lymphadenitis and possibly some types of cutaneous tuberculosis."

4 Edelston, B. G. Treatment of a Tuberculous Operation Wound by Local Application of Promanide Jelly, *Tubercle* **25** 108 (Nov-Dec) 1944

5 The British term for promin®

6 Hinshaw, H. C., and Feldman, W. H. Observations on Chemotherapy of Clinical and Experimental Tuberculosis, *M. Clin. North America* **29** 918 (July) 1945

Murphy,⁷ in a report on 11 patients treated with promin[®] jelly, stated, "Promin jelly applied topically does lead to eradication of the infection and to promotion of healing in varied forms of extrapulmonary tuberculosis"

Promin[®] jelly is sufficiently fluid to permit easy application and is of such consistency as to prevent rapid absorption, thus allowing continuous contact in a concentrated form with the open ulceration. This can explain the rapid healing as a direct bacteriostatic action on the myobacterium tuberculosis in these tuberculous "gummas"

Although this is only 1 case, the aforementioned favorable reports of other authors warrant experimental use of the drug in other cases of extrapulmonary tuberculosis rather than immediate internal medication with high doses of calciferol (crystalline vitamin D₂) with its possible attendance of serious complications in the heart, blood vessels, kidney and the like

I am now using experimentally 5 per cent promin[®] in jelly and in penetrating bases on the lupus vulgaris plaques in a 32 year old patient with scrofuloderma and disseminated lupus vulgaris and in 2 cases of lupus miliaris disseminatus faciei. There has been some improvement. A report on the progress of these cases will be submitted later

SUMMARY

Three tuberculous ulcerations in a Negress failed to respond to 6 units of roentgen rays filtered through 1 mm of aluminum. The ulcers healed in seven weeks after local applications of 5 per cent promin[®] jelly¹ and at the time of writing had remained so for two and one-half years. The good result is attributed to the bacteriostatic effect of promin[®] and to its slow diffusion in the tragacanth jelly base, thus allowing continuous contact with the myobacterium tuberculosis. The lack of recurrence or aggravation of the lesions is most likely due to the type of the ulcerations, classed as tuberculous gummas, since they appeared to be clinically and roentgenologically independent of any deeper tuberculous foci. Because of the rapid healing and the ease of application, it is recommended that promin[®] jelly be given a trial in cutaneous and other accessible extrapulmonary tuberculosis before other methods such as calciferol with its attending danger of toxicity, are used

219 East Nineteenth Street

⁷ Murphy, J. A. R. "Promin" in Tuberculosis. A Short Preliminary Review Accompanied by Short Clinical Notes of the Use of "Promin Jelly" (5 Per Cent) in Eleven Cases, M. J. Australia 2:310 (Sept. 8) 1945

PLASMA PROTEIN AND DERMATITIS

Preliminary Report

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AND

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DETROIT

WAR INEVITABLY brings into focus problems of nutrition. The recent conflict, because of its global character and attendant malnutrition, added great impetus to the already expanding science of nutrition. The United Nations Conference on Food and Agriculture¹ in May 1943 found the evidence convincing that malnutrition was "responsible for widespread impairment of human efficiency and an enormous amount of ill health and disease." Recent progress in the study of nutritional elements fires the imagination. Vitamins have been produced in pure and concentrated forms and their functions more clearly defined, the essential nature of fats has been demonstrated, and the role of proteins and minerals has been more fully clarified. But, more important, there has come an understanding of the deficiency state, with a fuller appreciation of the frequency with which these states impair tissue functions and man's usefulness. Unfortunately, the methods of diagnosis of nutritional abnormality remain inadequate, no more so, however, than were those for syphilis and tuberculosis not so many years ago. Most clinicians have been interested in the severe acute forms of malnutrition as invariably follows the ravages of war or the obvious end results of long-continued frank deficiencies as seen in pellagra, scurvy and the like. The time has arrived when the student of nutrition must be concerned with the submarginal states of deficiency, the chronic forms of malnutrition frequently beginning in early life, with their corrosive effect on human health. The incidence of such borderline states is undoubtedly large, notably in this country,

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¹ Final Act and Section Report, United Nations Conference on Food and Agriculture, Hot Springs, Va., May 18 to June 3, 1943, Washington, D. C., Government Printing Office, 1943, p. 61

as Jolliffe² stated that it has been clearly demonstrated by recent surveys that a large proportion of the American population has some degree of malnutrition

The extensive use of plasma in World War II and the recent work of Co Tui,³ Elman⁴ and others in the therapeutic use of amino acids has reemphasized the nutritional importance of proteins, especially with respect to normal processes of growth, shock, fluid balance, wound healing and tissue resistance. Decided impetus was given to these studies by the great technical advances that have been accomplished in recent years in plasma fractionation, notably with the properties of protein, their separation and purification and their biologic functions.

We are indebted to Cohn⁵ and his fellow workers for much of the newer knowledge of blood fractions. These workers developed a fractionation process which yields all the components of human plasma in five major fractions. In a detailed diagram the authors graphically portrayed the natural functions, clinical uses and separation in fractions of the plasma proteins. These plasma proteins are of at least two distinct varieties, the albumins and the globulins, differing mainly by the greater solubility of albumin in water. Globulin is further fractionated into fibrinogen and the alpha, beta and gamma globulins. Each of these fractions has certain characteristic physical properties and is associated usually with specific physiologic functions. As Cohn⁵ said, "the knowledge of blood proteins and their therapeutic value that has been gained in this war enables us to approach the future with a very different view than was possible a decade ago, to even the most far-sighted physician, who was taking advantage of all the scientific knowledge then available."

FUNCTION OF PROTEINS

Mulder,⁶ the Dutch chemist who in 1839 first suggested the term "protein," characterized it as "unquestionably the most important of all known substances in the organic kingdom." Lewis⁷ reviewed

2 Jolliffe, N, and Smith, J J. Nutrition in the Practice of Medicine, M Clin North America **27** 567, 1943

3 Co Tui. Some Clinical Aspects of Protein Nutrition, J Am Dietet A **22** 97, 1946

4 Elman, R. Maintenance of Nitrogen Balance by the Intravenous Administration of Plasma Proteins and Protein Hydrolysates, Physiol Rev **24** 372, 1944

5 Cohn, E J. Blood Proteins and Their Therapeutic Value, Science **101** 51, 1945

6 Mulder, G J. The Chemistry of Animal and Vegetable Physiology, in Mendel, L B. Nutrition The Chemistry of Life, New Haven, Conn, Yale University Press, 1923, p 16

7 Lewis H B, in Handbook of Nutrition, Chicago, American Medical Association, 1943, chap 2

much of the knowledge of proteins. The role of proteins in life and metabolism is manifold, they are essential components of both the cytoplasm and the nucleus of the body cell, they are important in determining the osmotic relations between extracellular and intracellular fluids, and the substances associated with the humoral resistance to disease are proteins. In addition, many enzymes have the properties of proteins, and some hormones are either proteins or are derived from proteins.

As the nature of the properties of protein unfolds, additional functions in body metabolism are being ascribed to it. There are, however, three generally accepted essential functions of proteins: (1) the building of body proteins, (2) maintenance of body fluid balance and (3) their role in immunity and tissue resistance.

1 Building of Body Proteins—Chemically, proteins are large complex organic molecules, which in the process of digestion are broken down into simpler chemical units (polypeptides) and eventually into the component amino acids. The amino acids are then absorbed and enter the portal and general circulation. In normal protein nutrition a major portion of the absorbed amino acids is used for replacing and building body and plasma proteins, and the remainder is deaminated chiefly by the liver, with the formation of carbohydrate and the production of nonprotein nitrogenous products which are excreted in the urine. Some twenty-two nutritionally important amino acids have been identified. Rose⁸ and his co-workers have shown that at least eight are indispensable for the maintenance of nitrogen equilibrium in young human adults for limited periods. An "essential" amino acid is one that cannot be synthesized by body tissues in sufficient amounts to meet its physiologic requirements and therefore must be obtained from ready made foods. It also means that the amino acids in question are necessary for some essential physiologic process. As yet, nothing is known of the quantitative requirements of essential amino acids in man. The biologic or nutritional value of proteins is dependent on their content of amino acids, particularly those that are essential. Generally speaking, proteins of animal origin and those from milk, eggs, fish and fowl are of higher biologic value than vegetable proteins, since they contain all the essential amino acids. In this connection, it is well to keep in mind that most foods rich in protein furnish nutrients other than proteins. They are generally among the best sources of the vitamin B complex as well as a good source of minerals and frequently of fats.

8 Rose, W. C., Hames, W. J., Johnson, J. E., and Warner, D. T. Further Experiments on the Role of Amino Acids in Human Nutrition, *J. Biol. Chem.* **148** 457, 1943.

Since proteins are the most important constituent of cytoplasm, the individual structure and function of the body tissues depend to a large extent on the normal anabolism of protein intake and protein reserves. Man can probably dispense with carbohydrate and possibly with fat, but life and normal growth are dependent on proteins or their constituents—the amino acids.

2 Maintenance of Body Fluid Balance Perhaps the next most important function of protein is the part it plays in the osmotic relations between intracellular and extracellular fluids. This hypothesis, suggested more than fifty years ago by Starling,⁹ explains why fluid flows back into the capillaries even though the capillary filtration pressure produces a constant outflow toward the tissue spaces. The dynamics of the circulation is dependent on the blood pressure and the osmotic pressure of the plasma proteins. Fluid is held within the blood vessels by the osmotic pressure, against the force of the blood pressure which tends to drive it into the tissues. Perfect maintenance of the balance between the fluid within the blood vessels and the extravascular fluid thus depends on the holding of the level of the plasma proteins at about 7 Gm per hundred cubic centimeters of plasma. Any decrease of proteins tends toward the passage of fluid into the tissues. The reduction of the plasma proteins may result from a wide variety of causes, and when the level reaches about 4 Gm per hundred cubic centimeters the differential between osmotic pressure and blood pressure is sufficiently low so that fluid passes out of the blood vessels.

3 Tissue Resistance and Immunity Still another function of protein metabolism is its role in the resistance of the organism to infection. Cannon,¹⁰ in a series of articles, has championed this theory and has shown that decreased protein reserves brought about by prolonged low protein diets leads to a definite decrease in specific antibody production in laboratory animals. He pictures antibodies as especially modified humoral globulins the formation of which is dependent on protein intake and protein reserve. In the human being, the association of famine with infectious diseases and the many examples of increased susceptibility to intercurrent infection, evidenced by patients with low protein levels, indicate a relationship between dietary factors and bacterial resistance. Cannon¹⁰ expressed the opinion that in recent

⁹ Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312, 1896.

¹⁰ Cannon, P. R. Antibodies and the Protein Reserves, *J. Immunol.* **44** 107, 1942; Protein Metabolism and Resistance to Infection, *J. Michigan M. Soc.* **43** 323, 1944.

years much evidence has accumulated to justify the conclusion that many important aspects of the problem of infection and resistance are essentially nutritional

ALTERATION OF PLASMA PROTEIN PATTERN

As the result of much work during recent years, it is evident that knowledge of the serum protein levels is of considerable significance in the diagnosis and treatment of many medical and surgical conditions, a clinical fact almost completely overlooked by dermatologists. The plasma proteins have achieved such clinical importance because, unlike tissue proteins, they are capable of clinical measurement. Such determinations were made at the beginning of the century, but it was not until the 1930's that they were extensively employed and only in recent years has their full application come to be understood.

Most illnesses and injuries are characterized by disturbances in protein metabolism as evidenced by a urinary excretion of nitrogen usually far above the normal. In many instances the extent of this altered catabolism of protein can be determined by measuring the concentration of the protein in the serum, as shown by the ratio of albumin and globulin present. In protein nutritional deficiency, the hypoproteinemia is the result of a reduction in the albumin fraction, since the globulin fraction exerts less than one-fifth the osmotic effect of albumin. Hyperproteinemia usually is characterized, however, by an increase in the globulin fraction.

HYPERPROTEINEMIA

A number of years ago Wu¹¹ called attention to the fact that total serum protein concentration may be increased to 9 or even 10 Gm per hundred cubic centimeters in kala-azar. This increase was found to be due to a rise in the globulin fraction. Since that time it has been observed that a number of disease states are characterized by an increase in the globulin fraction of the plasma. Hyperproteinemia, which is essentially hyperglobulinemia, is considered to exist when the serum globulin concentration is above 3 Gm per hundred cubic centimeters or when, in the absence of globulin determination, the total protein concentration is above 8 Gm per hundred cubic centimeters.

Furthermore, with few exceptions, whenever the globulin concentration is increased above normal, the total protein concentration is usually also increased above normal. Hyperglobulinemia may be due to increase in the normal globulin constituents, or to the presence of abnormal globulin or to both. It occurs in diverse clinical conditions, in many of which the cause is unknown.

11 Wu, H. A New Method for the Determination of Plasma Proteins, *J Biol Chem* **51** 33, 1922

Kagan¹² reported on 50 cases in which the condition was due to sixteen different causes, classified as diseases involving bone marrow, chronic infections and dehydration. Of these, a number are of interest to the dermatologists. They include Boeck's sarcoid, leukemia, tuberculosis, syphilis and lymphogranuloma venereum. It is interesting to note that the highest value for serum protein concentration obtained by Kagan was 10.1 Gm per hundred cubic centimeters in a case of monocytic leukemia, which diagnosis was proved by autopsy. He also found hyperglobulinemia in bacterial endocarditis, lupus erythematosus and periarteritis nodosa. Similar observations have been reported in dermatomyositis.¹³ Since these four conditions are generally fatal diseases and have a number of other clinical and pathologic similarities, the presence of hyperproteinemia may be found to be a significant feature. Kagan presents clinical data to support the theory that serum globulin is formed by the plasma cells in the reticuloendothelial system throughout the body. Aside from its role as an antibody, very little is known of the functions of globulin, although its concentration in some of these conditions may eventually prove a helpful diagnostic sign. Since hyperproteinemia in itself has not been proved to be harmful, its treatment at present would be unnecessary even if the proper procedure were known.

HYPOPROTEINEMIA

Just as hyperproteinemia is mainly an increase in the globulin component of plasma protein, so hypoproteinemia is essentially hypoalbuminemia. In health, with adequate intake of high quality protein, the body stores protein and production and protein wear and tear are in a nicely balanced or "steady" state, the dynamic equilibrium of Whipple.¹⁴ In the absence of disease these proteins can pass readily from plasma into cells and reverse without loss of nitrogen. Since during most illnesses there is an increase in protein catabolism, any decrease of circulating proteins tends toward the passage of fluid into the tissues, with the production of hypoalbuminemia. The perfect maintenance of this balance between the intracapillary hydrostatic pressure and the colloid osmotic pressure of the blood depends on the level of plasma proteins being held at about 7 Gm per hundred cubic centimeters of plasma. Satisfactory normal range for the concentra-

12 Kagan, B. M. Hyperglobulinemia, *Am J M Sc* **206** 309, 1943.

13 Janeway, C. A. The Plasma Proteins. Their Importance in Clinical Medicine and Surgery, *New England J Med* **229** 779, 1943.

14 Whipple, G. H. Hemoglobin and Plasma Proteins. Their Production, Utilization and Interrelation, *Am J M Sc* **203** 477, 1942.

tion of serum protein of adults, according to Peters and Eisenman,¹⁵ is 60 to 80 Gm per hundred cubic centimeters for total protein, for albumin 40 to 55 Gm per hundred cubic centimeters and for globulin 14 to 30 per hundred cubic centimeters. Youmans¹⁶ expressed the belief that emphasis should be given to the significance of values slightly below the arbitrary lower level of normal. He expressed the opinion that one is apt to be too much influenced by low serum levels encountered in patients with severe disease. In less ill, ambulatory patients, particularly in relation to nutritional protein deficiency, concentration, especially of albumin, though but slightly below the lower normal range, is apt to be significant. The resultant hypoproteinemia of protein deficiency usually shows a proportionate decrease in both albumin and globulin, though in cases of mild disease, the globulin may remain at the usual level or rise to a high normal or even slightly above normal.

PATHOGENESIS OF HYPOPROTEINEMIA

Hypoalbuminemia is the result of a number of causes, although more than one of these mechanisms often operate together.

1 Malnutrition The simplest, most obvious and commonest cause of protein deficiency is lack of protein in the diet. In addition, the deficiency may result from the ingestion of poor quality protein, that is, not containing all the essential amino acids, as is now regrettably the case in famine-stricken areas throughout the world, notably in India and China. Given a sufficient intake of quantity and quality protein, there are still many factors which may interfere with the ultimate delivery of adequate protein to the tissues. These include faulty absorption or utilization, increased breakdown of body protein and loss by diarrhea or renal diseases. Protein deficiency of itself may lead in time to actual edema of the intestinal mucosa, resulting in poor intestinal absorption, thus completing the vicious cycle.

2 Excessive Loss of Plasma—Hypoalbuminemia may be produced by any loss of plasma which the body cannot regulate or correct. Shock, hemorrhage and burns, all associated with reduced blood volume, are well known surgical examples of such loss. Peters,¹⁷ in a study of 2 cases of exfoliative dermatitis, found that the protein loss in the desquamated skin was pronounced in 1 patient, accounting for 40 per cent

15 Peters, J. P., and Eisenman, A. J. The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System in Diseases, *Am J M Sc* 186 808, 1933.

16 Youmans, J. B. The Clinical Detection of Protein Deficiency, *J A M A* 128 439 (June 9) 1945.

17 Peters, B. A. Exfoliative Dermatitis Treated with Cystine, *Lancet* 1 264, 1945.

by weight of his protein intake Mulholland¹⁸ studied a large number of patients with decubitus ulcers and found them to be associated with hypoproteinemia It is possible that persons with pemphigus¹⁹ and other extensive long-continued exuding dermatoses may suffer sufficient loss of plasma protein to produce hypoalbuminemia The loss of protein in exudates and discharges is a more serious loss than it would appear to be in terms of nitrogen alone, since it represents the loss of preformed protein

3 *Excessive Loss of Nitrogen* Normally a few grams of nitrogen are lost each day in the urine, largely from tissue and plasma proteins used up in the metabolic wear and tear In certain conditions, this destruction of protein becomes excessive and is revealed by large losses of nitrogen in the urine This has been shown by Hirshfield,²⁰ Levenson²¹ and others to occur regularly in burns In Levenson's series the condition in all patients with 10 per cent or more of the cutaneous surface involved in a third degree burn became a serious nutritional problem, because of the losses of nitrogen in the urine and from the burned surface Hirshfield showed that moderately or severely burned patients excreted more nitrogen in the urine than could be administered orally as protein without forced feeding This was in addition to the loss in the exudate Excessive loss of nitrogen occurs also after crushing injuries, certain surgical procedures, ether anesthesia and thyrotoxicosis

4 *Deficient Albumin Synthesis* Hypoalbuminemia is frequently encountered in hepatic disease²² Cirrhosis, catarrhal jaundice and toxic hepatitis, through impairment of hepatic function and attendant interference with normal gastric function, frequently are responsible for serious undernourishment and protein deficiency Studies in recent years of the relationship between plasma proteins and hepatic diseases have indicated that, in order to maintain efficient hepatic function, adequate protein supplies are necessary, and, conversely, in order to maintain normal plasma protein levels, the liver must be in good func-

18 Mulholland, J H , Co Tui, Wright, A M , Vemic, V , and Shaferoff, B Protein Metabolism and Bed Sores, *Am J Surg* **118** 1015, 1943

19 Mulvehill, W Serum Proteins in Dermatoses, *Arch Dermat & Syph* **49** 327 (May) 1944

20 Hirshfield, J W , Williams, H H , Abbott, W E , Heller, C G , and Pilling, M A Significance of the Nitrogen Loss in the Exudate from Surface Burns, *Surgery* **15** 766, 1944

21 Levenson, S M , Davidson, C S , Lund, C C , and Taylor, F H L The Nutrition of Patients with Thermal Burns, *Surg , Gynec & Obst* **80** 449, 1945

22 Davis, H A , and Getzoff, P L Hypoproteinemia in Surgical Diseases, *Arch Surg* **44** 1071 (June) 1942 Post, J , and Patek, A J Serum Proteins in Cirrhosis of the Liver, *Arch Int Med* **69** 67 (Jan) 1942

tional condition²³ Thus another vicious cycle is encountered, because the damaged liver cannot carry out its normal function of manufacturing proteins, which it ordinarily furnishes to the blood and which in turn protects it against damage

In the presence of hypoproteinemia, such conditions as chloroform anesthesia, biliary obstruction and treatment with heavy metals, results in more injury to the liver cells than occurs in well nourished persons Conversely, the injured liver cannot manufacture albumin as well as the normal one²⁴

TREATMENT OF HYPOPROTEINEMIA

Since the clinical significance of an increase in the globulin fraction is unknown, therapy of hyperproteinemia is unnecessary in the present state of knowledge The correction, however, of hypoproteinemia, while a comparatively recent achievement, is a therapeutic advance that is frequently more dramatic and brilliant than results accomplished in other forms of nutrition management Recent progress in the isolation and purification of amino acids, the relative ease of their parenteral use and the rapid progress in making them available for oral administration promise to make their use a routine method for ready correction of hypoalbuminemia, once the condition is recognized

Food—Good food taken by mouth is the most effective and satisfactory way to administer protein Increasing the amount of protein in a diet is one of the best general ways to improve a diet, for protein foods are usually good carriers of many other nutrients, such as vitamins of the B complex and minerals Ordinarily 150 Gm of protein per day is thought to be the upper limit of intake for the average-sized adult However, Eskimos are said to live on a normal intake of 500 Gm per day Many persons insist that they feel better with a high protein intake Further study will no doubt define the ceiling of intake similar to the maximum amount of vitamins necessary to restore a depleted patient as soon as possible In giving protein by mouth it is important to realize, first, that a large amount of protein must be ingested if one is to correct severe deficiency rapidly and, secondly, that the protein selected must contain a large proportion of essential amino acids

Plasma Transfusions—Plasma was accumulated in the war largely for the prevention and treatment of shock It has since found widespread use in civilian practice and offers an immediate and often life-

23 Plasma Proteins and the Liver, editorial, J A M A **116** 2855 (June 28) 1941

24 Madden, S C, and Whipple, G H Plasma Proteins Their Course, Production and Utilization, *Physiol Rev* **20**, 194, 1940

saving method of replacing plasma protein depleted by hemorrhage, burns and other acute diseases. The injected proteins, so far as they cannot readily pass through the kidney, increase the body's reservoir of plasma proteins and, since they do not easily traverse the capillary walls, increase the plasma volume by drawing water from the tissues into the blood stream.

Cohn⁵ said that as a sole source of protein plasma transfusions are unsatisfactory, because of the rapidity with which the protein leaves the circulation. Elman,²⁵ however, expressed the opinion that in nutritional hypoproteinemia one or more ordinary plasma transfusions are excellent supplementary procedures. He further suggested that such transfusions should be followed with parenterally administered amino acids.

Intravenous Injections of Protein Hydrolysates The use of proper mixtures of amino acids is really the only simple and practical method of correcting protein deficiencies by the intravenous route. In reality, it is a physiologic method of alimentation inasmuch as all protein food normally enters the circulation as amino acids. This newer procedure therefore simply offers a shortcut around the gastrointestinal tract by sparing not only digestion but also absorption. Furthermore, it introduces building stones of protein directly to the tissues where they may be picked up and quickly used wherever needed. As knowledge of protein deficiencies increases, so will the intravenous injection of amino acids. The practical details involved in preparing and giving amino acids intravenously have been solved. Reactions have been practically eliminated, and the solution is as simple to give as isotonic sodium chloride or dextrose solutions. Elman²⁶ encountered only 0.8 per cent of reactions in a series of 2,729 consecutive injections, none of which were severe. The speed of injection is important, as it is probable that the body cannot assimilate more than 25 Gm of amino acids per hour.

Oral Use of Amino Acids There have been several difficulties encountered in the oral use of amino acids, which have hindered their more extensive use. That they frequently provoke digestive disturbances is well known. From the practical point of view, expense, in the average case, has been a handicap. Similarly, many patients complain of the very unpleasant taste, as it frequently is impossible to mask the unpalatable features. All of these objections are rapidly being

²⁵ Elman, R. Protein Metabolism and the Practice of Medicine, M. Clin North America **27** 303, 1943.

²⁶ Elman, R. The Intravenous Use of Protein and Protein Hydrolysate, Ann New York Acad Sc **47** 345, 1946.

overcome, and protein hydrolysate combinations will, no doubt, in the not too distant future, be widely used in the oral management of hypoproteinemia

ROLE OF HYPOPROTEINEMIA IN DERMATITIS

Although hypoproteinemia has been observed extensively for the past decade, its importance is being recognized more and more. The concept of lowered plasma protein as a clinical condition is very young, and its association with delayed wound healing is even younger. The degree of hypoproteinemia does not have to be great to cause delay in the healing of wounds²⁷. A reduction of 15 per cent may lead to moderate delay, while a reduction of 25 per cent is severe enough to cause serious delay or complete failure of healing.

Its role in burns, wound healing, edema, decubitus ulcers and other conditions with which the tissue integrity of the dermis and epidermis is intimately related has been thoroughly studied in most branches of medicine except dermatology. A few years ago Mulvehill¹⁹ investigated serum proteins in fifteen different dermatoses and reported no change of significance in values for total proteins, serum albumin and serum globulin in any of the diseases considered except pemphigus. These observations seemingly ruled out a nutritional protein deficiency as a factor in all forms of dermatitis. However, the pronounced hypoproteinemia in the cases herein reported led us to inquire into the possibility of a like deficiency state in similar exudative conditions, particularly with the thought of possible therapeutic benefit to be derived from protein, plasma and amino acids as used so extensively today in other branches of medicine.

For centuries, a relationship between diet and cutaneous diseases has been recognized. The extent to which cutaneous diseases were interpreted to be the result of improper diet varied with the prevailing view of the medical profession at that time. The tendency to regard every cutaneous manifestation as a result of dietary indiscretion naturally caused the pendulum to swing so far that until recent years the dietary therapy of cutaneous disease had few supporters. The discovery of vitamins and their clinical efficiency once again focused attention on nutritional therapy. Progress has been rapid in the past ten years, and, while much remains to be learned, the addition of vitamin therapy has been a definite help in the management of a number of hitherto intractable dermatoses. Perhaps because of the emphasis and tremen-

²⁷ Koster, H, and Kasman, L. P. Relation of Serum Protein to Well Healed and Disrupted Wounds, *Arch Surg* 45:776 (Nov) 1942

dous progress in vitamin therapy, the importance of other elements has been overlooked, but regardless of the reason, there is a widespread failure on the part of physicians to recognize the extent and importance of protein deficiency in a great variety of diseases. In spite of reputed high nutritional standards, submarginal deficiency states and chronic forms of malnutrition are undoubtedly present in this country in serious numbers. It is with these borderline states that dermatology should be concerned, and it is possible that investigation of plasma protein changes of some dermatoses of obscure origin may open avenues of therapeutic approach as fruitful as has been the progress in vitamin therapy.

There is surprisingly little laboratory evidence available to support the theory that alteration in the pattern of the serum proteins influences the tissue integrity of the skin. Madden²⁸ has demonstrated that in the dog long periods (twenty-five to thirty weeks) of plasma depletion and basal diet intake remove much protein from body fluids and tissues. Associated with this protein depletion, the dog loses his appetite and may vomit some food. There was a loss of hair, and superficial ulcers of the skin developed in the gluteal region. A definite fall in the albumin-globulin ratio was noted. Similarly Kulehar²⁹ studied directly the effect of dehydration in rabbits on experimentally induced infections on their skin. He observed that the dehydration not only failed to influence unfavorably, even to the point of lethal exit, the course of the artificially induced infection but that many animals apparently checked their infections or at least the inflammatory manifestations disappeared as they were deprived of water. In the reverse direction, when water was restored, the inflammation once more took up its full and even exaggerated activity. This series of observations confirms for the skin the now well established concept that inflammatory reaction in the skin is profusely influenced by water content. Different methods, other than withholding water, have been used to reduce hydration of the cutaneous tissues: reduction of sodium chloride intake, as in the Gerson diet, a sharp reduction in carbohydrate, or a decided increase in the protein intake, the latter by its diuresis and by its influence on the osmotic pressure. Conversely, it could be assumed that hypoproteinemia by its influence on osmotic fluid pressure would result in overhydration with microscopic edema and reproduced inflammatory activity in these same rabbit skins.

28 Madden, S. C., Winslow, P. M., Howland, J. W., and Whipple, G. H. Blood Plasma Proteins: Regeneration as Influenced by Infection, Digestive Disturbances, Thyroid and Food Proteins. A Deficiency State Related to Protein Depletion, *Exper. Med. & Surg.* **65**: 431, 1937.

29 Kulehar, G. V., and Anderson, H. E. The Relation of Water Metabolism to Experimental Skin Infections, *Brit. J. Dermat.* **48**: 477, 1936.

Mulholland,¹⁸ studying protein metabolism and bed sores, came to a similar conclusion. He investigated a series of 35 patients with decubitus ulcers, observing that plasma protein concentration was invariably below the lower limits occurring in healthy persons. The extent and the depth of the ulcer seemed to be related to the level of this concentration. With low protein diets, nitrogen balance remained negative, loss of weight continued, plasma protein concentration was depressed and the ulcers did not heal. When a mixture of amino acids and dextrose was added to the unsatisfactory diet, the nitrogen balances were reversed, plasma proteins increased and the ulcers promptly healed. It is known that a certain amount of pressure applied to normal tissue for a sufficient length of time can cause necrosis of that tissue. In patients with protein malnutrition the tissues are so changed in character that it apparently takes a lesser amount of pressure for a shorter time to cause necrosis. It might be expected that when malnutrition reaches a certain point even the amount of pressure exerted by the recumbent body for the usual period of rest may cause tissue necrosis. Mulholland further reasoned that this tissue has undergone a "change of character." Apart from the light this study throws on bed sores, the implication that tissues, including skin, of patients with poor protein nutrition have this character of impaired viability is significant in connection with the entire problem of protein nutrition and its relation to dermatitis. It is furthermore well known that tissues of persons with hypoproteinemia have diminished healing powers.

Our attention was particularly directed to the possible therapeutic benefit of protein and its chemical components in a report by Peters¹⁷ on the successful treatment in 2 cases of dermatitis exfoliativa with cystine. One patient, who was losing about 40 per cent by weight of his protein intake in the desquamated skin, responded in ten days to 0.25 Gm of cystine hydrochloride given subcutaneously and 1 Gm of cystine by mouth daily. His general condition improved, the anasarca disappeared and the skin returned to normal. Unfortunately, he died two weeks later from other causes. The second patient received 1 Gm of cystine by mouth for twenty days with slow improvement and complete involution of the dermatitis in two months. Peters suggested that patients who lose large quantities of epithelium from any cause are liable to suffer from lack of sulfur-containing amino acids.

Mention was made by Goldsmith³⁰ of possible benefit from the oral administration of protein hydrolysates in 2 cases of exfoliative dermatitis. After the usual therapeutic procedures had failed, both patients showed a striking clinical improvement in a few weeks.

30 Goldsmith, N. R. Possible Benefit from Protein Hydrolysates for Exfoliative Dermatitis, *Arch Dermat & Syph* 55:397 (March) 1947.

Reporting on 6 selected cases of atopic eczema, with serum protein determinations, Drant³¹ reviewed the therapeutic results achieved with high protein diet and biweekly injections of autogenous serum. In addition, 4 of the 6 patients received biweekly intracutaneous injections of hapamine® (a chemical combination of histamine and despeciated horse serum globulin) and 2 were given endocrine therapy. Three of the 6 patients were apparently cured, as judged by one to two years' observation. The other 3 were not relieved. The author concluded that immunization with autogenous serum is efficacious when the albumin is high and the globulin fraction low and, conversely, when the globulin is high and albumin low immunization gives poor results.

Peters¹⁷ report suggested to us a possible therapeutic approach in a refractory case of arsenical exudative exfoliating dermatitis. When first seen the patient was seriously ill, but after five weeks' hospitalization she improved and was allowed to return to her home. Shortly after her discharge her condition became worse, and three weeks later she was readmitted. At the end of forty-seven days her exudation and exfoliation were worse, she had lost more weight and she was critically ill. Her serum proteins were albumin 2.13 Gm and globulin 4.01 Gm per hundred cubic centimeters. She was given a high protein, high carbohydrate and high caloric diet, 500 cc of plasma was administered and during the next three days two injections of protein hydrolysate were given. Improvement started on the third day with a rapid decrease in exudation and edema of the skin, the pruritus and exfoliation disappeared, and in two weeks she was discharged. At the time of reporting she had remained well for six months.

REPORT OF A CASE

History—V. S., a woman aged 29, was first admitted to Receiving Hospital, Wayne University Medical School, Nov. 29, 1945, because of a severe generalized dermatitis. During the subsequent ten months she returned with the same complaint on five occasions, after varying intervals. She was hospitalized a total of one hundred and fifty-seven days. The patient informed us that she had never been really well, and it was learned from her mother that she had had infantile eczema at 2 months, which continued in a severe form for several years, thereafter recurring at frequent intervals until the age of 9. From 9 to 19 she was comparatively free except for flexural involvement. From early life until the age of 18 asthma had been a distressing symptom. For the ten years prior to examination the attacks had been worse in the fall and for seven years prior to examination she had been annoyed with the usual symptoms of fall hay fever. During the previous four years her dermatitis had been continuous, with frequent unexplained remissions and exacerbations. A definite dislike for crowds was apparent, and the patient had always been a nervous person. She strongly suspected

31. Drant, P. Evaluation of Blood Protein and Factors in Atopic Eczema, *Pennsylvania M. J.* 49:1331, 1946.

foods as a causative factor and stated the belief that her unhappy marital state occasioned the "flare" of her eruption in recent years. Improvement was noted during the menses, but recently her periods had been irregular and on one occasion amenorrhea persisted for five months. She had been hospitalized at other institutions and treated by many physicians and in many clinics.

Examination—The patient was a woman of short stature who presented a generalized dermatitis, the most striking feature of which was the obvious evidence of scratching. Excoriations were numerous and were in various stages of evolution, many still oozing, some heavily crusted with serum and others covered with a dried seropurulent exudate. The intervening skin was moderately erythematous and desquamating. At the wrists, cubital fossae and popliteal spaces the skin was thickened and fissured. The entire skin was slightly edematous, with noticeable swelling about the joints and definite bilateral puffiness of the upper and lower eyelids. The right eye presented an iris prolapse through an old incision for cataract removal. The lens had also been removed from the left eye. There was a generalized and slight, but definite, superficial adenopathy.

Course—A diagnosis of chronic disseminated neurodermatitis (eczema, asthma, hay fever complex) was made and the usual laboratory examinations instituted. Results of these studies were all within normal limits, and the accepted local and systemic therapy for atopic eczema was inaugurated. This approach, together with bed rest, brought the expected relief from symptoms, and on Jan 15, 1946, she was sufficiently improved to be discharged to the outpatient department. On January 19 she applied for readmission, stating that two days after returning home the itching and burning recurred. Her condition was much the same as at the time of the first visit. On four subsequent occasions she improved with many and diverse therapeutic procedures, only to have an exacerbation shortly after returning to her home. During her numerous hospital visits she had been studied in practically all other departments, with little additional information. Allergy studies incriminated sea foods, house dust, chocolate and oranges.

The amenorrhea was thought to be due to "chronic prolonged systemic disease" or anterior pituitary deficiency. This clue was followed, with no evidence pointing to endocrine imbalance. In conjunction with the department of psychiatry, psychosomatic therapy was undertaken. When the patient was admitted for the sixth time, on September 3, additional history revealed the fact that for some days prior to the return of the dermatitis she would invariably experience symptoms suggestive of diabetes insipidus, namely, polyphagia, polydipsia and polyuria. Burning and itching of the skin would then develop, which was followed with a slight generalized edema of the skin, most pronounced about the face and joints. The specific gravity of the urine was found to be 1.005, the result of the urine concentration test was 1018/1002 and the urea determination 20 Gm per hundred cubic centimeters. The symptoms of a disturbed water balance, edema of the skin, results of urine dilution concentration tests and low serum albumin suggested a protein deficiency as the explanation of the obvious impaired tissue integrity of this patient's skin. Since a measure of success had been obtained in a case of severe extensive arsenical dermatitis exfoliativa with parenterally supplied plasma and protein hydrolysate, similar therapy was started in an attempt to furnish "building blocks" for protein fabrication. She was placed on a high protein, high carbohydrate diet and from September 12 to September 19 received intravenously 2 units of plasma and 3 units of the protein hydroly-

sate Five hours after the first injection of plasma the patient noted a decided decrease in burning and itching, and the edema of the face was less In forty-eight hours she was up and about and more comfortable than at any time during her hospitalization Her symptoms were entirely relieved, the edema had almost entirely disappeared and the oozing had stopped At that time another unit of plasma was administered, which was followed with polyuria and decided thirst The erythema subsided rapidly, and she felt much stronger During this period, water balance studies indicated a urine output which was increasingly greater than the intake Three units of the protein hydrolysate were given in the next ten days, with continued improvement in the patient's general condition and the state of her skin Urine specific gravity was 1.008 and serum protein albumin 3.6 Gm and globulin 2.58 Gm per hundred cubic centimeters She was discharged on October 19, with her skin normal except for flexural thickening and without symptoms It was recommended that she continue on a high protein, high carbohydrate diet Three weeks after leaving the hospital she had a mild "flare" of her dermatitis, which subsided in five days On Feb 13, 1947, we called the patient's home to suggest further studies, when it was learned that three weeks previously jaundice had developed and that there was some return of her eruption She had sought medical advice elsewhere and on February 5 had been operated on for a supposed common duct stone No stones were found, the gallbladder was removed, and a diagnosis of subacute inflammatory hepatitis was made Biopsy of the liver showed "subacute hepatitis superimposed on low grade cirrhosis" Her dermatitis became worse, she rapidly lost ground, and on February 11 she died with severe generalized edema of the skin and pronounced swelling of the left leg No autopsy was performed

COMMENT

We cannot as yet speak with certainty concerning the connection between impaired hepatic function and cutaneous diseases It is generally accepted, however, that certain eruptions, notably those of the exudative exfoliating type that follow intoxication with heavy metals, can be interpreted as being the result of complex deficiencies brought about by altered hepatic function In our patient with atypical dermatitis we can only assume such dysfunction, although the low serum protein level may be interpreted as resulting, at least in part, from deficient protein plasma production

In the patient with atopic eczema we have microscopic evidence not only of hepatic damage but of probable functional impairment of some chronicity, as shown by the low grade cirrhosis Thus a mild degree of hypoproteinemia, resulting from deficient albumin synthesis, may have been present for a considerable period, causing the edema and swelling of the skin which had been in recent years a regular feature of the eczematoid attacks As in Mulholland's cases, the skin had seemingly undergone a "change of character" resulting in impaired viability, and with the almost continuous and uninhibited scratching its altered powers of healing were further decreased

In atopic eczema it is believed that an intracellular reaction of antigen and antibody leads to a release of a histamine-like substance³². Histamine then increases capillary permeability and dilates the capillaries, allowing an exudate rich in proteins to escape into the extracellular spaces³³. If the plasma proteins were already lowered, this loss of circulating protein may throw the patient into a phase of obligatory edema until the colloid osmotic pressure of plasma becomes sufficient, in the remission stage, to draw fluid back from the interstitial spaces. The protein in the interstitial spaces must return to the blood via the lymphatic system to help resupply circulatory plasma. Therefore, it might be good therapy to give plasma mainly for its effect in increasing the plasma volume and colloidal osmotic pressure of the blood.

This would tend to relieve the edema by drawing interstitial fluid back into the circulation. The resultant decrease in edema would also decrease the interstitial pressure. Thus decreased tissue pressure would mechanically allow the collapsed lymphatic vessels to reopen and return protein from the interstitial spaces more rapidly back into the circulation, hence improving its healing powers and aiding its viability. Also, the injection of plasma will assist the liver in its manufacture of albumin and temporarily compensate for the protein deficit. Since the liver has great recuperative powers, it may be possible in this way to "hold the fort" in the interim. The subsequent intravenous administration of amino acids furnishes building stones of protein directly and immediately to the cutaneous tissues, where they may now be picked up and quickly used wherever needed. So that this reparative process may be continued, it is essential that a high protein diet be continued together with an increased amount of protein-sparing carbohydrate.

An additional 6 patients with an exudative dermatitis and significantly lowered plasma protein levels have been treated with this regimen. Two seriously ill patients succumbed before treatment was completed. Another, with an exuding nummular eczema suffered an immediate intensification of pruritus after plasma, which was followed with a general erythema and some edema of the face. This reaction subsided in twenty-four hours, but treatment was discontinued. A fourth man with a history of eczema since childhood presented a severe eczematoid dermatitis of the hands, which had resisted treatment for one year. He was found to be sensitive to house dust, grass and trees. Attempted desensitization over a period of two months

32 Lewis, P. *Clinical Science, Illustrated by Personal Experiences*, London Shaw & Sons, Ltd, 1934

33 Dale, H. H., and Laidlaw, P. P. Histamine Shock, *J. Physiol.* **52** 355, 1918

failed to influence his eruption. During the administration of plasma a decided angioneurotic-like edema of the face appeared, and treatment was discontinued. However two days later improvement occurred and in a week his eruption was almost entirely gone. Two months later only slight lichenification remained.

In 2 additional patients both of whom were still under observation at the time of writing striking improvement was obtained. A man aged 34 gave a history of eczema since the age of 15. For the previous six years he had had repeated attacks at times generalized of an exudative exfoliating dermatitis. Since 1941 he had been hospitalized ten times. In addition to dietary therapy, he received 1 000 cc of plasma and five injections of protein hydrolysate. In two weeks he was discharged with little dermatitis. When seen one month later he was still free of his eruption.

The other improved patient was a man aged 43, who said that his eczema had started at the age of 29. He had been hospitalized three times in the previous six months. His present visit to the hospital was occasioned by a severe bullous reaction to a sulfonamide drug. Two injections of 500 cc of plasma in twenty-four hours followed with two injections of protein hydrolysate resulted in rapid improvement but the patient insisted on leaving the hospital. When contacted a month later his dermatitis was limited to the cubital fossae. Six months later there had been no return of his atopic eczema.

SUMMARY

A case of intractable chronic disseminated neurodermatitis treated with high protein high carbohydrate diet and parenterally administered plasma and a protein hydrolysate is reported. The response was rapid and dramatic, but unfortunately, the patient died four months later after abdominal surgical treatment. Mention is made of a case of arsenical exfoliating exudative dermatitis which responded to similar therapy after other treatment had failed. Also, 2 patients with chronic atopic eczema with exudation were promptly benefited by the aforementioned therapy. Obviously, no conclusions can be drawn from these few cases but a possible therapeutic approach is suggested in those cases of resistant disease in which significantly lowered protein plasma levels are encountered. The theoretic action of protein plasma and protein hydrolysate in dermatitis is discussed.

In an attempt to clarify further the role of serum proteins in dermatitis a series of correlative laboratory studies on a representative number of patients with chronic exudative exfoliating eruptions has been inaugurated. Since serum protein determinations may be mis-

leading in the absence of fluid balance studies, these investigations will include studies of weight changes, intake and urinary output, hematocrit, nitrogen balance and red and white blood cell counts

Since we strongly suspect hepatic impairment, in the metabolism of protein, as a fundamental alteration in certain chronic exuding and exfoliating erythrodermas, investigation of hepatic functions as they relate to the production of hypoproteinemia will also be undertaken

ABSTRACT OF DISCUSSION

DR FRANCIS W. LYNCH, St Paul While the presentation by Dr Keim and his co-workers is not the first dermatologic discussion of plasma proteins, it is a milestone because it is the first extensive consideration of therapeutic possibilities in this field. They have emphasized that the number of cases studied is too few to allow conclusive decisions, even though the results of treatment were highly encouraging. It should be noted that the treatment is not just by injection but that the authors urge a diet high in protein and with added carbohydrates. Most workers in this field regard eating as the best method for provision of proteins in any case in which the intestinal tract is anatomically intact, after study of war prisoners some doubt the existence of the vicious cycle with protein deficiency leading to poor absorption. In starved prisoners, food was found to be the most acceptable source of protein.

If added protein is desired, one may consider combining intravenous administration of protein hydrolysates and transfusions of human plasma and even of whole blood. Plasma is probably the most effective, though it may be deficient in one or several essential amino acids.

Kremen has shown that the giving of protein hydrolysates may leave the body in negative nitrogen balance, unless very large amounts are used or plasma is added. There is some thought that whole blood should also be added. It is likely that treatment should be continued for ten to fourteen days before one decides that it has been without value. In patients seriously ill with exfoliative dermatitis or eczema, there should be at least some benefit from increased formation of globulins for use as antibodies against infectious complications. Much additional study is needed to determine whether increased protein intake has a specific beneficial influence on the cutaneous cellular metabolism and the disturbed fluid balance seen in eczematous persons or whether therapeutic responses are due to nonspecific elevation of healing powers known to be lowered in the presence of protein deficiency.

The authors point out the newer evidence that many Americans are victims of deficiency diseases, and there is little doubt that diets are deficient for many dispensary and public hospital patients and even for some private patients. Much remains to be learned about the importance of impaired hepatic function in relation to protein deficiency. Dermatologists have been slow in utilizing newer techniques for demonstration of less severe impairments of hepatic function. We should not allow continuance of this defect in our knowledge, nor should we remain ignorant of the probably disturbed patterns of serum proteins in various dermatoses. From where in the pattern of serum proteins come the humoral antibodies of atopic persons? Do they differ in urticaria and eczema? Perhaps the proteins are different, and thus there is in the production of eczema less need for the histamine effect on capillary dilation and permeability.

Fortunately, the authors promise to help remedy some of our defective knowledge in this field. A small but important point is the question whether there is any specificity as to the particular amino acids needed for normal development of epithelium. There is no lack of problems for dermatologic investigation. Shall we leave this work for the internists to do when they find time, or shall we return to our clinics and hospitals stimulated to expand the start made by Dr Keim and his associates?

DR FRANK C COMBES, New York. My interest in serum proteins began when I suggested to Dr Mulvehill that he investigate the subject especially regarding the variation of serum proteins in pemphigus vulgaris. Proteins are interesting substances and became increasingly important during the war during meatless days. Relatively little is known about them. It is known that the human body is incapable of synthesizing them from simple organic substances. Furthermore, the human body is unable to store proteins in the sense that it can store carbohydrates and fats. Therefore, it is necessary that every person have a sufficient and balanced amount in his daily diet. Studies have also shown that it is essential that proteins, and especially the amino acids, be properly balanced, since in the absence of one or two of the latter, the body is unable to assimilate and utilize the others and may even excrete them unchanged.

Hypoproteinemia is found in many dermatoses, especially those that are chronic, such as pemphigus, exfoliative dermatitis, pellagra, pityriasis rubra and all types of varicose ulcers and ulcers of diabetic origin. I have often thought that hypoproteinemia might be due in part to dietary deficiencies, since so many of the patients are restricted as to the type of food ingested. Not infrequently patients with allergy who show no improvement following lengthy adherence to elimination diets recover promptly on ingestion of all foods with utter disregard for their allergies.

DR LOUIS A BRUNSTING, Rochester, Minn. There are two points that I should like to emphasize briefly in discussion. In cases of exfoliative dermatitis of long standing, regardless of causation, there is often a secondary anemia as well as a depletion of the proteins in the blood without a significant alteration of the albumin-globulin ratio, in contrast to that which occurs in cases of sarcoidosis or disseminated lupus erythematosus. As to therapeutic measures in such cases, I believe that a word of warning is in order concerning the use of pooled plasma. In this report the jaundice developed about one hundred and twenty days after the administration of pooled plasma and the patient died of hepatic disease. Homologous serum jaundice is a form of acute hepatitis, perhaps of virus origin, which follows the receipt of human blood, plasma or some of its derivatives, and it may appear after an incubation period of forty to one hundred and eighty days. Unless an emergency exists, I prefer the use of fresh whole blood to pooled plasma when such supportive treatment is indicated.

DR JASPER LAMAR CALLAWAY, Durham, N. C. I should like to point out that unless nitrogen balance studies and blood volume studies are made, most of the current plasma protein determinations will not mean much. Often the plasma will maintain a high level at the expense of the tissue fluids. Therefore, in order that figures have meaning in studies of plasma proteins, there must also be blood volume and nitrogen balance studies.

DR DONALD M PILSBURY, Philadelphia. I should like to recount briefly an involuntary experiment which occurred during the war with allied military personnel recovered after the German prison camps were overrun. Many thousands of these persons had, of course, been seriously starved and were suf-

fering from decided protein deficiency. My colleagues and I were interested in examining them to determine what this starvation had done to them, and I may say that the only change which I think one can say with certainty occurred was decreased resistance to infection, which some thought was due to vitamin deficiency. There were certainly few patients who had flare-ups of cirrhosis during their stay in the prison camps.

DR NORMAN N EPSTEIN, San Francisco. I should like to emphasize Dr Brunsting's warning about the use of plasma in the treatment of disease. In general, I think that there has been a tendency to discontinue its use because of the real danger of infectious hepatitis following the use of plasma obtained from persons who have had a history of jaundice even months or years previously. I am sure that the authors are aware of that, but I do think that it is important to emphasize that plasma should not be used too readily in the treatment of disease.

DR PAUL A O'LEARY, Rochester, Minn. The dangers of pooled plasma have recently been called to our attention by the bacteriologists and internists interested in infectious hepatitis. It has been demonstrated that the virus causing infectious hepatitis may be transmitted in extremely weak dilutions. A hypodermic syringe should not be used on more than 1 patient even though the needle is changed, because the organism may be transmitted in well diluted solutions such as cocaine. This has necessitated a change in our technic of intravenous therapy and minor surgical procedures as done in the office.

DR HARTER L KEM, Detroit. I am grateful for the generous discussion. We all, of course, recognize the possibility of virus hepatitis in using plasma. However, thousands of plasma injections were used in military service with relatively few accidents. Virus infection occurs on the average from two to six months after the plasma has been given, and since our patient's jaundice appeared approximately three months after the use of plasma it may have been an example of virus infection. However, it seems to me more probable that the jaundice was the result of factors other than the treatment utilized.

I agree with Dr Callaway that fluid balance studies are essential, since serum protein determinations may be misleading in their absence. Such studies together with other essential data will be included in the final paper. Admitting the limitations and possible dangers, we, as dermatologists, should investigate further the possible relationship of plasma proteins to various types of dermatitis. All branches of medicine, notably surgery, are using protein therapy extensively. While diagnostic methods are still inadequate and therapeutic management cumbersome, I do think that this approach offers great possibility of assistance in the management of a number of recalcitrant dermatoses.

DERMATITIS OF THE HANDS DUE TO INGESTED ALLERGENS

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AND

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CONSECUTIVE cases of dermatitis, chiefly or exclusively affecting the hands, 388 in number, seen in private practice, have been studied and classified etiologically as examples of dermatitis due to (1) external physical or chemical agents acting as a primary irritant or allergen, with or without secondary infection, (2) primary external infection with virus, bacterium, fungus or other parasite, (3) internal chemical disorder induced by ingested or injected medication, nutritional or endocrine derangement or ingested food allergen, (4) systemic or focal infection, including pustular bacterid, (5) distant dermatitis elsewhere on the body, such as tinea pedis or varicose ulcer, with secondary manifestations on the hands, and (6) specific disease of unknown causation, such as psoriasis, lichen planus, nummular dermatitis, seborrheic dermatitis, keratoderma climacterium or Darier's dyskeratosis. Other varieties of dermatitis of the hands include (7) malformation, such as epidermolysis bullosa and (8) neoplasm, such as senile keratoses or hemangiosarcoma of Kaposi, but such cases were not considered in these statistics. We concerned ourselves, for the purpose of this essay, with cases ascribed to class 3.

IDENTIFICATION OF A CLINICAL ENTITY

Thirty, or 7.7 per cent, of the 388 cases did not have the characteristics of classes 1, 2, 4, 5, 6, 7 or 8. They were not examples of psoriasis, lichen planus, epidermolysis bullosa or any other specific disorder and they did not respond to careful avoidance of external chemical and physical agents, to chemotherapy intended to combat the specific organisms found by culture, to elimination of ingested and injected medications, to correction of nutritional and endocrine disorders or to elimination of systemic or focal infection. Because the 30 patients showed cutaneous changes strikingly similar to those seen in so-called atopic dermatitis as it affects other cutaneous areas, they were placed tentatively in class 3, and the role of ingested food allergens was eval-

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uated This group of 30 patients presented characteristics which seem to constitute a clinically recognizable entity, with distinguishing features as follows

- 1 Localized areas of excoriation are seen accompanied with erythema or lichenification where partial healing has occurred
- 2 All visible changes are explicable as effects of finger nail excoriations alone
- 3 The scratching occurs while the patient is asleep
- 4 The dorsum of the fingers or hands or the ulnar surface of the wrist are the only sites involved

RECOGNITION OF ALLERGENIC FOODS

To demonstrate whether ingested foods do or do not play a role requires the use of a reliable method of testing individual foods and of interpreting the effect of such foods on the dermatitis, so that failure to cure by an effort to eliminate causative ingesta is not due to inaccuracy inherent in the method employed

Skin testing was adjudged not to be a reliable method, for dermatitis, if related to foods at all, is due to the actual ingestion of them, and the dermatitis of the patients under discussion was present on the hands and not on the back or arms where cutaneous tests are commonly performed The unreliability of cutaneous tests for food allergy is common knowledge¹ The single food additive diet² is considered to be more reliable While it causes the patient for a short time more privation than the multiple choice elimination diets, such as described by Rowe³ and Urbach,⁴ yet these persons, who have suffered dermatitis for periods ranging from one to thirty-four years in the present series and have exhausted many therapeutic efforts, readily accept this privation In the single food additive diet, all foods and medication are taken away, then a single new food is given for twenty-four hours,

1 (a) Rinkel, H J Food Allergy Role of Food Allergy in Internal Medicine, *Ann Allergy* 2 115-124 (March-April) 1944 (b) Rowe, A H Evaluation of Skin Reactions in Food Sensitive Patients, *J Allergy* 5 135-147 (Jan) 1934 (c) Sulzberger, M B, and Rostenberg, Jr Practical Procedure in Investigation of Certain Allergic Dermatoses, *J Allergy* 6 448-459 (July) 1935 (d) Flood, J M, and Perry, D J Role of Food Allergy in Eczematoid Dermatitis, *Arch Dermat & Syph* 55 493-506 (April) 1947

2 Winston, B H, and Sutton, R L, Jr Urticaria Detection of Ingested Allergens, the Single Food Additive Diet, *Practitioner* 160 347-352 (May) 1948 Sutton, R L, Jr, and Winston, B H The Detection of a Food Causing Allergy, Kansas City, Mo, The Beal Book Bindery, 1947

3 Rowe, A H Elimination Diets and the Patient's Allergies, Philadelphia, Lea & Febiger, 1941

4 Urbach, E, and Gottlieb, P M Allergy, ed 2, New York, Grune & Stratton, Inc, 1946

or longer if deemed necessary. The skin is examined each day prior to the addition of another food to determine the presence of any change attributable to the food last tested by the eating of it. Thus, a specific ingested allergen is identifiable immediately and with precision, with avoidance of the uncertainties of the multiple choice elimination diets. Conversely, ingesta suspected of being allergens, but which are not, can clearly be demonstrated to be nonallergenic. The time required for identification of ingested allergens is short as compared with their tedious and difficult identification by the use of multiple choice elimination diets. The single food additive diet resembles the strict trial diets employed by Flood and Perry.⁵

OBJECTIVE INDICATIONS OF SPECIFIC FOOD INTOLERANCE

Cutaneous changes conceivably capable of resulting from an ingested allergen are erythema, papulation, vesiculation, pustulation, exudation, scaling, whealing or traumatization induced by the pruritus provoked by the allergen. The last, excoriation of the dorsum of the fingers or hands, was, in the 30 cases, a more constant and objectively definitive observation than vesicles, pustules or oozing. The presence of recent excoriations is, in our experience, readily recognized and can be more accurately timed in relation to ingestion of test foods than the age of vesicles or pustules. A recent excoriation exhibits a bright red base, while an older and healing lesion is covered by a crust. Our procedure entailed the careful examination of the hands to determine the presence of new bright red gouged out lesions each day after the ingestion of a new food. If such new lesions were found, the new food was tentatively considered to be allergenic and was not eaten again for at least five days, after which it was retested. If excoriations again followed its ingestion, it was considered to be a proved allergen and was thereafter excluded from the diet for at least several weeks. Meanwhile the process of testing one new food a day was continued.

CRITERIA OF SPECIFIC INTOLERANCE

To test the relationship of cause and effect of an ingested food to the dermatitis, the following criteria were established:

1. Contactant interference was eliminated for the substances allowed to touch the affected skin were limited to air, water, cotton and petrolatum,⁶ and not any medication was applied, bland, antiseptic or other.

5 Flood and Perry,^{1d} Recurrent Vesicular Eruptions of the Hands Due to Food Allergy, *J Invest Dermat* **7** 309-327 (Dec) 1946.

6 Sutton, R. L., Jr. Contact Dermatitis. Simplification of Therapy and of Search for Causes, *J Missouri M A* **44** 481-484 (July) 1947, Contact Dermatitis. Practical Management and Identification of Cause Without Patch Testing, *Arch Dermat & Syph*, to be published.

2 Therapeutic intervention was eliminated, for no roentgen or ultra-violet rays were used and no internal or external alteratives were allowed

Having established conditions under which the unadulterated influence of diet alone might be estimated, the dermatitis was judged due to ingested allergens if (1) the disease disappeared on the single food additive diet, (2) the disease was reproduced by the addition to the diet of a sufficient quantity of specific foods so detected as allergenic and (3) the disease disappeared again on the elimination of these specific foods

When persons with erythematous papulovesicopustular dermatitis of the fingers and hands were under this management, they did not fulfil all of these criteria of dermatitis of the hands caused by foods. But when persons exhibiting the distinguishing features aforementioned, suggestive of atopic dermatitis, and showing nocturnal excoriation on the dorsum of the hands, were placed under this management, they did satisfy all of these criteria

ILLUSTRATIVE CASES

CASE 1—H L, A white woman aged 61, a housewife, was seen Feb 23, 1948, with dermatitis of the hands of four years' duration. The disease was limited to the dorsa of the hands and consisted of fairly well circumscribed erythematous areas with decided excoriation, crusting and lichenification. She would wake during the night to find herself digging at the skin, she has found blood on her finger nails on waking. There was no history of allergic rhinitis or asthma.

Previous dermatologic management included an assortment of ointments, pills, injections, 1,500,000 units of penicillin given intramuscularly, roentgen ray therapy, 775 r, tonsillectomy for possible focal infection and isolation of the hands from external chemicals for weeks, all without control of the dermatitis. Her best symptomatic relief was obtained with crude coal tar paste and roentgen therapy, but these did not prevent recurrences.

On March 8 she was placed on a single food additive diet. The use of external chemicals was prohibited, no internal medication was given, roentgen and ultra-violet rays were not used. Her sole treatment consisted in the removal of all foods and then eating a single new food component at intervals of not less than twenty-four hours. Within six weeks she was free of disease. The ingestion of pork or of corn was followed by pruritus and excoriation. Water, salt, cane sugar, rice, beef, chicken, bananas, beets, green beans, raisins, oranges, egg yolk, egg white, peaches, milk, white potatoes, cabbage, oatmeal, wheat, bread, fat (spry®), tuna fish, grapefruit, tea, peas and salmon were tolerated. Cutaneous tests were performed for comparison with the following results: results for raisins, oranges, egg yolk, cabbage, lima beans, corn and pork were 1 plus, results for peaches were 2 plus, results of all other foods tested were negative. The result of a single attempt to demonstrate serum reagins to pork by means of the Prausnitz-Kustner technic was negative.

There were numerous occasions during the use of the single food additive diet that the patient stated that she was emotionally upset and that she thought "nerves" might be the cause of her dermatitis. It was noted that if she ate a food to which she was hypersensitive at a time when she was emotionally upset,

pruritus was more intolerable and excoriation was more pronounced. However, when she was severely upset emotionally and did not eat a food to which she was allergic, there was no pruritus or excoriation.

CASE 2—J R, a white man aged 30, a railroad machinist helper, was seen Nov 4, 1946, with dermatitis of the hands of nine months' duration. The disease was limited to the dorsa of the hands and consisted of fairly well circumscribed erythematous areas with decided excoriation, crusting, exudation and moderate lichenification. He was always worse in the morning and would wake during the night to find himself gouging out the skin until it bled. He did not suffer with allergic rhinitis or asthma.

Dermatologic management consisted in his leaving his job, restricting contact of the affected areas to air, water, cotton and petrolatum, intramuscular injection of 6,000,000 units of penicillin, eradication of foci of infection by extraction of infected teeth, tonsillectomy and prostatic massages, intramuscular injection of 10 Gm of streptomycin, the use of 3 drops of potassium arsenite solution (Fowler's solution) three times a day with daily increment for ten days, the use of 300,000 units of vitamin A orally and 1 Gm of cevitamic acid subcutaneously daily, ketogenic diet, the use of sulfadiazine, and roentgen radiation, 450 r. These measures were unsuccessful in controlling the dermatitis.

The result of the trichophyton test at 1 to 30 dilution was negative. The result of the oidiomycin test at 1 to 100 dilution was slightly positive. Culture from the hand lesion on Feb 7, 1947 grew *Streptococcus faecalis*. Another culture from the hand lesion on March 5, after the use of streptomycin, showed only hemolytic *Staphylococcus aureus*, coagulase positive. Culture of prostatic secretion grew hemolytic *Staph aureus*, *Strep faecalis* and the colon bacillus.

On April 28 he was placed on the single food additive diet. The use of external chemicals was prohibited, no internal medication was given, and roentgen and ultraviolet rays were not again used. Ingestion of all substances was stopped, and then only one new food was eaten at intervals of not less than twenty-four hours. Within five weeks he was free from disease. The ingestion of carrots, chicken or white potato was followed by pruritus and excoriation. The ingestion of eggs for three consecutive days resulted in pruritus and excoriation. As recently as Feb 27, 1948, coffee was found to remain allergenic, but hypersensitivity to the other foods had subsided by November 1947.

CASE 3—J A, a white man aged 46, a machinist, was seen Nov 21, 1946, with dermatitis of the hands of six months' duration. The disease was limited to the dorsa of the hands and consisted of fairly well circumscribed erythematous areas, with pronounced excoriation, exudation, crusting and moderate lichenification. He did not suffer with allergic rhinitis or asthma.

Dermatologic management consisted in his leaving his job, restriction of contacts of the affected areas to air, water, cotton and petrolatum, eradication of foci of infection by extraction of infected teeth and tonsillectomy, ingestion of multivitamin capsules daily, intramuscular injections of 3,600,000 units of penicillin, roentgen therapy, 600 r, and the local application of methylrosaniline chloride, aluminum acetate solution and crude coal tar. These measures were unsuccessful in controlling the dermatitis. The best symptomatic relief was obtained with crude coal tar paste and roentgen therapy but these did not prevent recurrences. There was decided improvement of the dermatitis immediately following tonsillectomy at which time the food intake was reduced in variety and quantity, but the improvement was lost when the throat healed and a customary diet was resumed.

On May 19, 1947, he was placed on the single food additive diet. No medication was used externally or internally. The ingestion of potato or orange juice was followed by pruritus and excoriation. These were removed from his diet, and by June 20 he was free of disease.

CASE 4—P C, a white woman aged 53, a housewife, was seen July 25, 1947, with dermatitis of the hands of thirty-four years' duration. The disease was limited to the dorsa of the hands and consisted of circumscribed erythematous areas with excoriation, crusting and lichenification. Excoriation occurred during her sleep. Dental roentgenograms revealed no infection, and tonsillar tissue had been completely removed. Gastric analysis showed no free hydrochloric acid after the injection of histamine. The red blood cell count was 4,320,000, the hemoglobin was 11.5 Gm, the color index was 0.86, and the volume of packed red blood corpuscles was 40 per cent. There was no history of allergic rhinitis or asthma.

Previous dermatologic management included roentgen therapy to the limit of safety (at least 1,500 r), an assortment of ointments, pills and injections and the limitation of contacts of the affected areas to air, water, cotton and petrolatum. These measures were not curative, although temporary symptomatic relief followed roentgen therapy.

On August 4 she was placed on the single food additive diet and was given dilute hydrochloric acid orally, no other medication was used externally or internally. Within six weeks she was nearly free of disease. The ingestion of coffee, asparagus, orange, grapefruit or pineapple was followed by pruritus and excoriation. She was not willing to forego these foods, and, as of the time of writing, she continued to suffer exacerbations when she ate them.

CASE 5—B B, a white woman aged 29, a saleswoman, was seen June 18, 1946, with dermatitis of the hands of eighteen months' duration. The disease was limited to the dorsa of the hands and the ulnar surface of the wrist and consisted of fairly well circumscribed erythematous areas, with pronounced excoriation, exudation and crusting. She would wake during the night to find herself digging at the skin. There was a history of seasonal allergic rhinitis, but no asthma.

Previous dermatologic management included the use of antiseptic ointments, eradication of foci of infection, the use of penicillin intramuscularly and roentgen therapy. These measures were unsuccessful in controlling the dermatitis.

On May 13, 1947, she was placed on a single food additive diet. No medication was used externally or internally. The ingestion of corn or corn products was followed by pruritus and excoriation. These were removed from her diet, and by June 18 she was free of disease.

CASE 6—D M, a white woman aged 30, a housewife, was seen April 17, 1947, with dermatitis of the hands of eight years' duration. The disease was limited to the dorsa of the hands and fingers and consisted of fairly well circumscribed erythematous areas with excoriation, crusting and lichenification. There was a history of allergic rhinitis, for which she had been for one year under the management of an allergist, who thought that ingestion of peas and chocolate and inhalants were causative of the rhinitis. Although her allergic rhinitis did improve under his management, dermatitis of the hands did not improve.

Dermatologic management included the avoidance of contactant irritants, the eradication of foci of infection which entailed tonsillectomy, the use of penicillin intramuscularly and roentgen therapy. Culture yielded hemolytic *Staph aureus*. These measures were unsuccessful in controlling the dermatitis.

On July 9 she was placed on the single food additive diet. No medication was used externally or internally. The ingestion of corn and corn products, lima beans

or butter was followed by pruritus and excoriation. These were removed from her diet, and by August 20 she was free of disease.

CASE 7—F. R., a white man aged 31, a printer, was seen Aug. 13, 1947, with dermatitis of the hands and fingers of two years' duration. The disease was limited to the dorsa of the hands and fingers and consisted of fairly well circumscribed, erythematous areas with excoriation, exudation, crusting and lichenification. He would wake to find himself gouging out the severely pruritic skin. There was no history of allergic rhinitis or asthma.

Previous dermatologic management included the application of many and various medications, penicillin given intramuscularly and sulfadiazine orally. He quit his job, and contacts on the affected areas were restricted to air, water, cotton and petrolatum. These measures effected little change in the dermatitis.

On August 23 he was placed on the single food additive diet. No medication was used externally or internally. Ingestion of coffee or chicken was followed by pruritus and excoriation. These were removed from his diet, and by October 10 he was free of disease.

DIAGNOSIS AND TREATMENT

Dermatitis of the hands due to ingested allergens may occur without the presence of dermatitis in the flexural areas usually involved in atopic dermatitis. Pruritus present in dermatitis of the hands due to ingested allergens is of that paroxysmally extreme intensity seen in more widespread atopic dermatitis, so that deep excoriation occurs particularly during sleep when self restraint is at a minimum. Relief of pruritus during a food-induced paroxysm does not seem to occur until the skin is gouged raw into the dermis. Rubbing and light scratching do not relieve it. Dermatitis of the hands not caused by ingested allergens may be accompanied with pruritus and scratching, but no matter how much the patient may complain of these symptoms, they are not intense enough to induce gouged out lesions of the skin. All the visible cutaneous disease present in dermatitis of the hands proved to be due to ingested allergens is that which is expected from nothing but repeated mechanical finger nail excoriations, that is, the telltale gouged out lesions, erythema and lichenification. These are almost entirely confined to the dorsum of the hand. This type of dermatitis of the hands characterized by excoriations may be distinguished morphologically from (1) cases of erythematous papulovesicopustular lesions of the fingers and palms with peripheral extension and central clearing which improve with treatment with sulfonamide drugs and sometimes with penicillin,⁷ (2) cases of pustular bacterid⁸ of the palms, (3) cases of vesicular and scaly "id" eruptions⁹ due to tinea pedis, (4) cases of primary tinea of

⁷ Winston, B. H. Dermatitis of the Hands, *Arch. Dermat. & Syph.* **57**: 357-367 (March) 1948.

⁸ Andrews, G. C., Birkman, F. W., and Kelly, R. J. Recalcitrant Pustular Eruptions of Palms and Soles. *Arch. Dermat. & Syph.* **29**: 548-563 (April) 1934.

⁹ Peck, S. M. Epidermophytosis of the Feet and Epidermophytids of the Hands, *Arch. Dermat. & Syph.* **22**: 40-76 (July) 1930.

the hands, (5) cases of erythematovesicular contactant dermatitis and (6) painful ulcerative and crusted dermatitis due to streptococci

The influence of contactant irritants, local secondary infection, foci of infection, emotions, roentgen rays, antibiotics and inhalant hyposensitization procedures is of interest. Mechanical and primary chemical irritants, such as soap and wool cuffs, may aggravate the lesions, but elimination of these does not result in cure of patients with food allergies. They act in a manner analogous to the spilling of lemon juice or alcohol on a laceration to produce stinging and burning and yet are not causes of the pruritus-induced lacerations. Despite the presence of local secondary infection, healing is usually obtained in cases of food allergy without resort to antiseptics, although occasionally healing may be hastened by the brief use of antiseptic, usually not more than twenty-four to forty-eight hours. The eradication of foci of infection, which is a desirable procedure, does not result in cure in cases of food allergy, but it was observed that when this required surgical procedures interfering with eating for several days the dermatitis frequently improved during the period of restricted food intake. Emotional disturbances, "nerves," are not primarily causative, although they may serve as aggravating factors. Case 1 is illustrative. The patient expressed the belief that "nerves" were the cause of the dermatitis. With the use of the single food additive diet, it was found that when she was emotionally upset and ate an allergenic food the pruritus was more intolerable, but when she was emotionally disturbed and did not eat any allergenic food there was no pruritus and therefore no excoriation. We frequently tell patients that itching will make a person "nervous" but "nervous" persons do not always itch. A course of roentgen therapy nearly always provides symptomatic relief for a short time while it is being given, for it reduces the inflammatory response and alters local tissue hypersensitivity, but the disorder recurs after its discontinuance. The time required for recurrence seems to vary to some extent with the total dose of roentgen rays administered. Many of the patients in this series had already received maximal roentgen therapy to safe limits, yet still showed dermatitis. The antibiotics do not alter the course of the disorder except for their effect on secondary infection. Determination of inhalant allergens and hyposensitization was not undertaken, although 1 patient (case 6) was undergoing such therapy for an allergic rhinitis without improvement of her dermatitis. Rowe¹⁰ has reported benefit from inhalant hyposensitization procedures

10 Rowe, A. H. (a) Dermatitis of the Hands Due to Atopic Allergy to Pollen, *Arch. Dermat. & Syph.* **53** 437-453 (May) 1946, (b) Atopic Dermatitis of the Hands Due to Food Allergy, *ibid.* **54** 683-703 (Dec.) 1946

in some cases, and he has obtained positive cutaneous reactions to inhalants which were not responsible for any demonstrable clinical allergy in other cases

EVALUATION OF RESULTS DURING DIETARY INVESTIGATION

Difficulty in the interpretation of the results obtained with the single food additive diet may occur. Although ingestion of an allergenic food usually causes an exacerbation within twenty-four hours,^{1a} a longer time may be required. Occasionally repeated ingestion of the food may be required before a quantity sufficient to cause allergic symptoms is attained. The development of symptoms only when a sufficient quantitative accumulation of ingested allergen has been attained may explain the variation in response that is sometimes found to an allergenic food and the apparent increase in tolerance after it is withdrawn for a time. Sometimes pruritus resulting from the ingestion of an allergen may persist for seventy-two hours instead of merely twenty-four hours. Thus, whether ingestion of an allergen provokes delayed symptoms or provokes unusually persisting symptoms, foods tested subsequently would tend to be indicated as allergens when they actually are not. The physician is placed on the alert for these possibilities when three or four consecutively administered new foods are followed by excoriations. When pruritus and excoriations follow the experimental ingestion of new foods under test conditions for ten consecutive days, it is likely that food is not the cause of the disorder.

When a method of testing foods, and of interpreting the results of tests, itself permits a variety of interpretations, the investigator can be misled into interpreting changes consistent with the use of the method as being cause and effect, and inconsistencies as being due to other factors. When we attempted to determine the role of ingested allergens in erythematous papulovesicopustular dermatitis of the hands, the high incidence of inconsistencies that required a search for factors other than food allergy led us to withhold judgment of the role of food allergy in these cases. When determination of the role of ingested allergens is reported to require several years,^{10b} we become even more reluctant to accept the cause and effect relationship in these cases.

SUMMARY AND CONCLUSIONS

Of 388 instances of various kinds of dermatitis of the hands, 30 presented characteristics which seem to constitute a clinically recognizable dermatitis due to ingested food allergy, the distinguishing features of which are

1. Localized areas of excoriation are seen accompanied with erythema or lichenification where partial healing has occurred

2 All visible changes are explicable as effects of finger nail excoriations alone

3 Scratching occurs while the patient is asleep

4 The dorsum of the fingers or hands or the ulnar surface of the wrists are the only sites involved

5 Removal of contactant irritants or eradication of focal infection does not result in healing

6 Elimination of the causative ingested allergens does cure

Ingested allergens are identified by the eating of not more than one new food a day and the subsequent observation of gouged out excoriations indicative of specific allergenic paroxysmal pruritus. Cutaneous tests are not reliable. Benefits from diet were not obtained in vesicopustular or nummular conditions. Not more than 8 per cent of cases of dermatitis of the hands in this series was due to ingested allergens.

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ABSTRACT OF DISCUSSION

DR JOHN F MADDEN, St Paul Certain questions come to mind when one thinks about dermatitis caused by the ingestion of foods. Do food allergens cause a clinically recognizable entity? Winston states that they do on the hands. Livingood reported a group of cases of dermatitis due to ingested food allergens at the American Dermatological Association meeting in California in April 1948. His cases showed many types of dermatitis varying from acute vesicular weeping lesions to the chronic lichenified type reported by Winston. It is logical to assume that the type or acuity of the dermatitis would depend on the amount of allergen ingested and the degree of sensitivity of the patient, as well as other less obvious factors.

Does the dermatitis occur in one particular location on the skin in all patients each time that any food allergen is ingested? Livingood's patients had many locations involved, including eyelids, face, neck, axillas, feet, buttocks and breasts. The dermatitis tended to recur in certain sites in some persons, but varied greatly from patient to patient. In Winston's cases the eruption occurred or flared repeatedly only on the hands. It is agreed that the hands are the commonest site involved but I question whether the fixed type of eruption on the hands is not the exception rather than the rule in dermatitis caused by or related to food allergens.

Are food allergens the sole cause or one of several factors in cases of dermatitis in which they are concerned? Winston found food allergens to be the sole cause in his cases, and the dermatitis healed when the offending food or foods were removed from the diet. Livingood found food only one of several factors in half of his cases, and the dermatitis healed in only half of his patients when the food allergens were withdrawn. Other factors, such as soap, occupation, emotion, age of the patient and the eruption and season, should play some part in changing the course of dermatitis due to food allergens on the hands and elsewhere.

What is the best way to determine whether food causes or plays a part in causing dermatitis? It seems to be agreed that scratch and intradermal tests are of little or no value. The single food additive diet advocated by Winston appears to be the best and most rapid method.

The interval between the ingestion of the food allergen and the beginning of the exacerbation should vary in different patients and in the same patient at different times. In Livingood's cases the interval between ingestion of the food allergen and the appearance of cutaneous symptoms varied from within thirty minutes to forty-eight hours. In 3 cases exacerbations did not occur until the food allergen had been eaten on six consecutive days.

Winston's patients cooperated with him and were free from eruption in a very short time. Most persons find that the patients on any restricted dietary regimen do not cooperate at all or only for a short time. Long periods of hospitalization are generally required, and this is expensive and usually prohibitive.

The possibility of external contact, stressed by Sulzberger and Peck, must be carefully eliminated. This calls for absolute honesty on the part of the patient or twenty-four hour daily observation, usually in a hospital.

Winston's paper is stimulating, but it might seem to oversimplify the very complex problem of cutaneous reactions to food allergens.

DR MAURICE J. RUTTER, Milwaukee. There is much confusion existing regarding the classification, causation and therapy of inflammatory eruptions of the hands. The most intriguing part of this presentation is the fact that Dr. Winston has been able to separate, on clinical grounds, a certain type of dermatitis of the hands which could be relieved by food elimination diets. These cases he was inclined to classify with the atopic dermatitis group. Dermatologists have long considered the problem of foods as causal factors in eruptions of the hands. Unfortunately, their attempts to evaluate by history, cutaneous tests and trial elimination diets the importance of foods have not been too successful. Cutaneous tests for foods have been notoriously misleading. Elimination diets have been difficult to follow, so much that some investigators have stressed the need of hospitalization for this procedure.

Perhaps dermatologists are ignoring a not infrequent cause of dermatitis, not only of the hands but elsewhere, because of the practical difficulties of using elimination diets for the average patient. It would be of interest to know how Dr. Winston managed his elimination diet, whether a dietitian was required and the average period of investigation needed to identify the offending food. If his results and, I might add, those of other recent reports can be confirmed, the rest of us will have to find some way of overcoming the difficulty of using elimination diets in the average office practice.

In the final analysis we must not lose sight of the fact that it is difficult and often impossible to explain the most cases of dermatitis of the hands in terms of a single cause. The hands are frequently the site of inflammatory changes that are termed eczematization, a readily recognizable clinical picture. These inflammatory changes are dependent on insults to the skin of the hands from a wide variety of interrelated factors. Some such compound factors have been aptly expressed by Stokes as "contact, contact infective and infective allergenic." There are many others.

DR GEORGE ANDREWS, New York. I congratulate Dr. Winston on a fine contribution to this subject. His figures are somewhat in accordance with the figures in a paper by Dr. Maurice Barnes and myself, "An Analysis of 200 Cases of Recalcitrant Eruptions on the Hands and Feet in 1940" published in the *Southern Medical Journal* and read at the annual meeting of the society in St. Louis that year. In that analysis of recalcitrant eruptions of the hands and feet we found that 6 per cent were caused by food and diet. Some of these eruptions were on the dorsum of the hands, but a great many of them were also on the palms. I am not too much impressed by the determination of the cause of

the eruption on the hands by morphologic aspects or distribution. This is all right in contact dermatitis, but in some of the other eruptions that can be very misleading I have in mind several patients who have been in the armed forces and disabled for months or years because of recalcitrant eruptions on the palms which were treated as fungous infections. In these cases no fungi could be demonstrated microscopically. They would usually say that they had never been on a diet and had not been treated for food allergy. The condition in a fairly large percentage of those few patients, I suppose as many as 6 or 8 in all, if they were put on elimination diets, would clear up entirely within a couple of weeks. Food tests were of little value, although I used to do food tests after the eruption cleared up, hoping that they might help us identify the exact allergen.

The most direct and practical attack on the problem is as follows. In persons who have such eruptions, in whom no fungi could be found, who show no signs of bacterid or psoriasis, who have used various antibiotic ointments without benefit and who wear white cotton gloves day and night for about two weeks without any benefit, there may be some internal causative factor. The best thing to do is to put them on Alvarez' elimination diet. Alvarez described an easy practical diet, which is more simple than the Rowe diet. The diet should be maintained for three weeks, which seems to me better than the day to day method. One does not know whether an offending food may make the skin worse the following hour or the following day or three or five days later.

DR MARION B. SULZBERGER, New York. This is a careful and lengthy piece of work. I admire the amount of industry, thought and attention that has gone into it and also the way Dr. Winston has presented the material in a clear concise fashion. I have gathered that the observations are actually in contrast to and, I might even say, in contradiction to those of previous observers whose works concerning ingested foods in hand eruptions have been cited. If I understood correctly, it was stated that in none of the cases of vesicular eruptions of the hands, oozing, crusting or nummular eczema types or pustular or pustulovesicular eruptions of the hands and in none of the eruptions of these types on both the hands and the feet could he show that foods played a significant role or a determining role or were even definite trigger factors. That, of course, is in contrast with the observations described by Rowe, Flood, Perry, Livingood and others, who have all found foods to play a role in cases of precisely the aforementioned forms of hand eruptions. After this observation, what, then, have Dr. Winston and Dr. Sutton found on the positive side? They found that foods play a role in producing exacerbations of pruritus, or perhaps even in producing an eruption, in some cases of what appears to me may be a localized form of atopic dermatitis which remains confined to the dorsa of the hands. I think that this fits well with the original conception of the flare-ups in atopic dermatitis, namely, that ingested foods and ingested or inhaled or even externally contacted "protein" allergens can and do produce paroxysmal localized or generalized itching in some cases.

Can there be cases of sharply localized atopic dermatitis confined to fixed areas, such as the dorsa of the fingers and hands, or must atopic dermatitis of the hands always have its other classic localizations as well? I am inclined to believe there exist exceptional cases in which there is localized atopic dermatitis of one or a few sites and that in these the exposure to ingested allergens can play a role in the production of exacerbations of itching and scratching and dermatitis.

However, in studying these cases I am confronted with the same difficulties in food elimination which were mentioned by Dr. Madden and Dr. Reuter and many others. In the patients, both of my office and my clinic, it is difficult for

me to approach the problem of even classic atopic dermatitis with properly executed and evaluated elimination diets

DR JAMES M FLOOD, Sayre, Pa When I started my studies in 1944, I was stationed at an Army General Hospital, and there it was possible to hospitalize patients for long periods of time and observe them carefully Since returning to civilian practice, it has become necessary to find some practical approach to the problem of dermatitis of the hands, especially related to food allergy In analyzing the cases my co-workers and I studied, on strict trial diets, we obtained a list of foods which we felt had low reactor indexes or seldom caused any trouble We instructed the patients to stay on the diet for a period of one week I think that this diet offers a good test as to whether the condition is one of food allergy or not If the patient is sensitive to any of the foods on the list, he will immediately become worse If he is not sensitive to any of this group, he will become better within a week's time

At this time the patients are allowed to add one food every other day The reason for using the forty-eight hour interval rather than twenty-four hour interval is that we found some patients who react in thirty-six hours rather than twenty-four hours

The list of foods we use are salmon, beef, cabbage, ry-krisp,[®] cherries, pears, prunes, tea, salt and sugar We have extended the use of this diet to other cases of eczematous dermatitis, and I believe that now I have several cases of very typical nummular eczema due to food allergy and several cases of localized neuro-dermatitis

DR H V ALLINGTON, Oakland, Calif I believe that there still will be a large number of cases of eczema of the hands in which it will be difficult to determine whether the cause is of internal or of external origin One procedure which I know has been discussed in the past but which I think is worth while emphasizing is the use of a diary If one can enlist the cooperation of a patient in keeping an accurate written record of the activities and events covering a period of twenty-four hours preceding a flare-up, it will frequently lead to helpful information I ask patients to write what they eat, in detail, both with and between meals They are also asked to record what they handle, either at work, in the home or in the garden I also ask them to note any drugs taken or any intercurrent illness Occasionally, for example, hand eczema will flare in association with an infection of the upper part of the respiratory tract A flare coincident with an attack of hay fever or asthma may suggest pollen allergy

Ideally, such records should be kept over a period covering several exacerbations Then, by comparing them, one may find some factor common to the period preceding each flare which will be etiologically important I know many patients will not cooperate fully and some not at all However, some clue may be discovered by this means which will guide further study in the right direction

DR GEORGE W BINKLEY, Cleveland I would like to hear some elaboration of the method that Dr Winston and Dr Sutton use in their elimination diet As I see it, there are two methods There is the rapid one, wherein one gives nothing for twenty-four hours except a dose of castor oil and some water, and then gives one food, such as milk Of course, cows' milk is a frequent allergen, and one may find a prompt reaction A slower elimination diet has been developed by Dr Albert Rowe My associate and I rarely achieved success with the Rowe elimination diet However, at present, we are combining the elimination diet of Flood and Perry pears, prunes, beef, salmon, cabbage, sauerkraut, and so forth, with local treatment, and we are encouraged We find that it is permissible to use external

therapy, such as a small dose of roentgen rays, if the condition is rather exudative. We use a solution of permanganate and tripeleennamine hydrochloride cream and other topical therapy unhesitatingly, because the response to these is so fleeting and so evanescent that one cannot confuse the response that comes with the actual elimination of the protein allergens. Topical treatments are often discontinued at the end of seven days, when we find that the patients have actually eliminated their allergens. Then we start the simple daily additive diet. Usually it is found that the patient is allergic to only two or three protein foods. In addition to the definite cutaneous reactions to single foods, there might be one or two foods that give doubtful reactions. In that case we ask the patient to use the suspected food later and in a larger amount.

DR BERNARD H. WINSTON, Kansas City, Mo. Dr Sulzberger is correct in stating that this paper is concerned solely with the role of food allergens in the production of pruritus of the hands and not with the production of erythematous papulovesicular dermatitis of the hands. This is because in persons with erythematous papulovesicular dermatitis of the hands it was not possible to fulfil the criteria of (1) disappearance of the dermatitis on the single food additive diet, (2) reproduction of the dermatitis by the addition to the diet of a sufficient quantity of specific foods so detected as allergenic and (3) disappearance again on the elimination of these specific foods, without the use of any external or internal medication.

The length of time necessary for pruritus to develop following ingestion of an allergen has varied from twenty minutes to forty-eight hours. Pruritus has persisted for as long as sixty hours. This does not invalidate the method. The food for the second twenty-four hour interval is initially falsely indicted as an allergen, but this is corrected on retesting one week later.

Hospitalization is not necessary for the use of the single food additive diet. No other elimination diet equals its accuracy. The use of a food diary is a guessing game by comparison, and it is inadequate.

STORY OF THE ORIGINAL "PORCUPINE MEN"

Classic Descriptions of Ichthyosis Hystrix

WILLARD L. MARMEZAT, M D
CLEVELAND

AMONG the congenital anomalies of the skin, there are few which hold greater fascination for dermatologists, the medical profession in general and even for the populace at large than the extreme forms of the peculiar type of giant nevus with horny, hypertrophic prolongations, extending over a large area of the body the condition commonly called ichthyosis hystrix. When presented to a group of dermatologists, the patient with ichthyosis hystrix, more often than not, comes in for his full share of attention a thorough familial interrogation, a scrutinizing observation and, after the initial palpation by the observers, the inevitable return of a number of them for that "second feel." The pathologist, with keen interest, turns to histology to see for himself, just as Unna first saw, the nevoid structure of the dermatosis. And, certainly, the countless curious at the circus side show enjoy the sight of the nevoid "porcupine man" as much as that of the sclerodermatous "stone man," the ichthyotic "fish lady" and the rest of the galaxy of unfortunates with ectodermal diseases.

Because these reactions of curiosity are the first and the simplest noted in the human mind, I have often been led to wonder about the first recorded case of ichthyosis hystrix. Who was the original "porcupine man"? Where was he first seen? What were the theories and reactions of the doctors of his day? The trail leads back more than two centuries to a group of intriguing reports which form the basis for this historical investigation.

The first of these appeared in the *Philosophical Transactions* for the year 1733¹. Of its author, John Machin, I have no information other than that he was a secretary to the Royal Society and a professor of astronomy. The report follows:

"An Extract from the Minutes of the Royal Society, March 16, 1731 containing an uncommon Case of a Distempered Skin, by John Machin, Sec R S and Prof Ast Gresh"

From the Department of Dermatology and Syphilology, Western Reserve University School of Medicine and University Hospitals

¹ Machin J. An Uncommon Case of a Distempered Skin, *Phil Tr Roy Soc* London 37:299-301, 1733

"A country labourer, living not far from Euston-Hall in Suffolk, shewed a boy (his Son) about Fourteen Years of Age, having a cuticular Distemper, of a different kind from any hitherto mentioned in the Histories of Diseases

"His Skin (if it be so called) seemed rather like a dusky coloured thick Case, exactly fitting every Part of his Body, made of a rugged Bark, or Hide, with Bristles in some Places, which case covering the whole excepting the Face, the Palms of the Hands, and the Soles of the Feet, caused an appearance as if those parts alone were naked, and the rest clothed. It did not bleed when cut or scarified, being callous and insensible. It was said he sheds it once every Year about Autumn, at which time it usually grows to the Thickness of three Quarters of an Inch, and then is thrust off by the new Skin which is coming up underneath

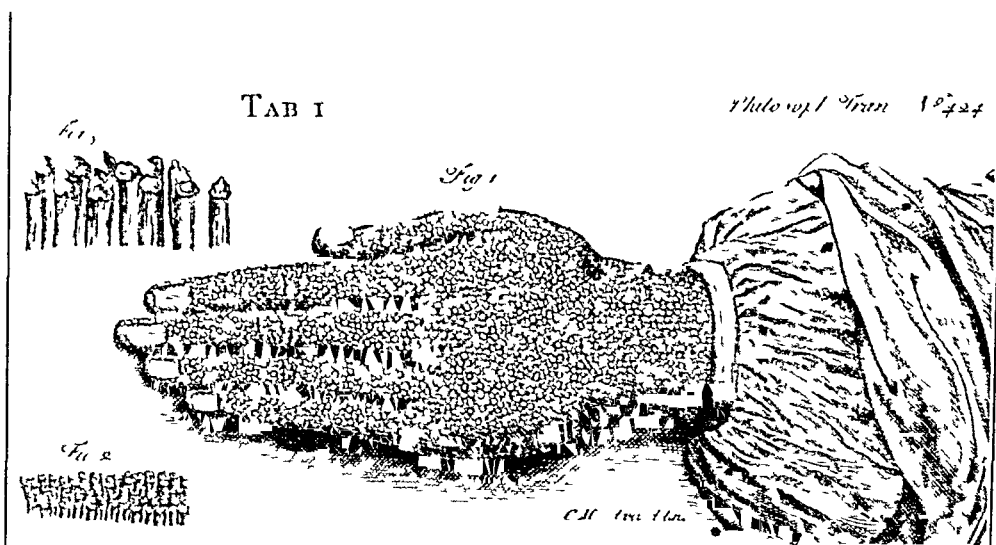


Fig 1—Plate accompanying Machin's report. The original legend follows: "Fig 1 Represents the back of the Boy's Hand. Fig 2 Represents a Portion of this extraordinary Epidermis which was probably a Prolongation of the Nervous Papillae grown to about the Size of common Twine Packthread, and these standing as close together as the Bristles in a Brush seemed like them, to be all shorn off even, and of the same Length, viz about half an Inch above the Skin. Fig 3 Shews some of these Bristles, or Stumps, magnified, where it is visible that some of them are flat at Top, others concave, some pointed like a Cone, and others very irregular."

"It was not easy to think of any Sort of skin, or natural Integument, that exactly resembled it. Some compared it to the Bark of a Tree, others thought it looked like Seal-Skin, others like the Hide of the Elephant, or the Skin about the Legs of the Rhinoceros, and some took it to be like a great Wart, or Number of Warts uniting and overspreading the whole Body. The bristly Parts, which were chiefly about the Belly and Flanks, looked and rustled like the Bristles or Quills of an Hedge-Hog, shorn off within an inch of the skin.

"His face was well featured, and of a good Complexion, if not rather too ruddy, and the Palms of his Hands were not harder, or in worse Condition than is usual for Workmen or Labourers. His Size was proper for his Age, his Body and Limbs streight and excepting as to this Deformity, well shapen.

"This rugged Covering gave him no Pain or Uneasiness, unless that sometimes after hard Work, it was apt to start, and cleave, and cause a Bleeding And notwithstanding the unusual disposition of his Humours to form so strange an Integument, his natural Excretions were said to be in the ordinary Course and Manner, without anything remarkable attending them

"The Father knew of no Accident to account for this distempered Habit But said that his Skin was clean at Birth as in other children, and so continued for about seven or eight weeks, after which, without being sick, it began to turn yellow as if he had the Jaundice, from which by degrees it changed black, and in a little time afterward thickened, and grew into that State it appeared in at present That he has been in Health from his Birth, and hath no sickness at the Season when he sheds it He further said, that his Mother had received no Fright, to his knowledge, whilst she was with Child, and Hath born him many other children, none of which have ever had this, or any other unusual Distemper or Deformity" (Fig 1)

Machin died in 1751 Exactly how closely he followed the case is not known However, in the *Philosophical Transactions*, in 1755, there appeared a supplemental report on the same case² This paper is noteworthy in that it showed that this nevoid dermatosis is not incompatible with general well-being, and, more important, by following the condition into the second generation and grasping at the genetic aspects of possible familial transmission of the condition, the author could not help but speculate on the alarming possibilities for future generations of mankind This document follows in part

A Supplement to the Account of a distempered Skin, published in the 124th Number of the Philosophical Transactions By Mr Henry Baker, F R S

"Read Jan 23, 1755—" As more than four and twenty years are now past since this account [Machin's original observation] was given, and the person therein mentioned is still alive, and was lately shewn at London, by the name of the Porcupine-man, with a boy in the like condition, both which I saw, and examined, some farther knowledge of him may not, I hope, be thought undeserving the attention of this Royal Society

"His name is Edward Lambert He is now forty years of age, a good-looking, well-shaped man, of a florid countenance, and when his body and hands are covered, seems nothing different from other people But except his head and face, the palms of his hands, and bottoms of his feet, his skin is all over covered in the same manner as in the year 1731, which therefore I shall trouble you with no other description of, than what you will find in Mr Machin's account abovementioned, only begging leave to observe, that in this covering seemed to me most nearly to resemble an innumerable company of warts, of a dark-brown colour, and a cylindric figure, rising to a like height, and growing as close as possible to one another, but so stiff and elastic, that, when the hand is drawn over them, they make a rustling noise

² Baker, H A Supplement to the Account of a Distempered Skin, Phil Tr Roy Soc London 49 21-24, 1755

"When I saw this man, in the Month of September last, they were shedding off in several places, and young ones, of a paler brown, succeeding in their room, which, he told me, happens annually in some of the autumn or winter months, and then he commonly is let blood, to prevent some little sickness, which he else is subject to whilst they are falling off. At other times he is incommoded by them no otherwise, than by the fretting out his linen, which, he says, they do very quickly and when they come to their full growth, being then in many places near an inch in height, the pressure of his clothes is troublesome.

"He has had the small-pox, and been twice salivated, in hopes of getting rid of this disagreeable covering, during which disorders the warting came off, and



Fig 2—Plate accompanying Baker's report. His original legend follows "Mr George Edwards, Librarian of the College of Physicians, having lately drawn, and etched on a copper plate, the hand of this boy, in such manner, as to shew the palm free from these excrescencies, and its other parts covered with them, and also a company of the excrescencies, as they appear where largest, a copy of the said plate, which I was favoured with by him, is now presented with this account."

his skin appeared white and smooth, like that of other people, but, on his recovery, soon became as it was before. His health at other times has been very good during his whole life.

"But the most extraordinary circumstance of this man's story, and indeed the only reason of my giving you this trouble, is, that he has had six children, all with the same rugged covering as himself. The first appearance whereof in them, as well as in him, came on in about nine weeks after birth. Only one of them is now

living, a very pretty boy, eight years of age, whom I saw, and examined, with his father, and who is exactly in the same condition, which is needless to repeat. He also has had the small-pox, and during that time was free from this disorder.

"It appears therefore past all doubt, that a race of people may be propagated by this man, having such rugged coats or coverings as himself and, if this should ever happen and the accidental original be forgotten, 'tis not improbable they might be deemed a different species of mankind a consideration, which would almost lead one to imagine, that if mankind were all produced from one and the same stock, the black skins of the negroes, and many other differences of the like kind might possibly have been originally owing to some such accidental cause" (Fig 2)

Baker's speculations concerning a future race of "porcupine men" later seemed well on their way to fruition. When Edward Lambert's son in turn, had two sons, John and Richard, with generalized horny excrescences, as had the father and grandfather, great interest in the Lambert family became manifest. Interestingly enough, the dermatosis had passed from father to son to grandsons, sparing the daughters in three generations. John and Richard Lambert became celebrated on the Continent and were widely exhibited and studied. The fact that their condition was different from ordinary ichthyosis was readily apparent. Experiments on the chemical composition of their epidermis were performed by numerous dermatologists. Complete reports on the Lambert family through successive generations were published by Tilesius von Tilenau,³ in Germany, and by Buniva, in France.⁴ Additional observations on this family were reported in England as late as 1834.⁵

The Lambert family of "porcupine men" spanned a century and excited the interest of dermatologists of many countries and several eras. There are few, if any, comparable incidents in the history of descriptive dermatology.

The Allen Memorial Library, Cleveland, and the historical division of the United States Army Medical Library made available the exceedingly rare and valuable books used in this study.

3 Tilesius von Tilenau, W. G. Ausführliche Beschreibung und Abbildung der beiden sogenannte Stachelschwein Menschen aus der bekannten Englischen Familie Lambert oder Porcupine Man, Altenburg, 1802.

4 Buniva, M. Particularites les plus remarquables de deux corn-écailleux Anglais nommes Jean et Richard Lambert, observes a Turin en fevrier et mars de l'an 1809, Mem Acad Imp d sc 18:364-402, 1809-1810.

5 London M & S J. September 1834, pp 969-970, cited by Raver, P. A Theoretical and Practical Treatise on Diseases of the Skin, Philadelphia, Corey & Hart 1845 p 352.

Clinical Notes

DERMATITIS FROM "PRELL" SHAMPOO

Report of a Case

C C CARPENTER, M D

SUMMIT, N J

Shampoos composed of many new types of detergents have recently been placed on the market for public use. Among these is "Prell radiant creme" shampoo, the active cleansing agent of which consists primarily of alkylsulfate¹. In general, these detergents are considered to have a low index of sensitization. Although use of the sulfated alcohol shampoos is now common and widespread, there has not been a corresponding increase in reports of irritation from them². As a search of the literature failed to reveal any previous reports of a dermatitis from this substance, it was believed that a short report of such an occurrence would be of interest.

REPORT OF CASE

J S B, a white woman aged 46, a hospital laboratory technician, was first seen Aug 28, 1947, with a severe weeping and crusted dermatitis of the face, scalp and neck. Except for occasional mild, localized neurodermatitis of the nuchal region and fungous infection of the toes, there had been no previous history of irritation of the skin.

The present eruption began within two days after "Prell" shampoo had been used for the second time. Three weeks before the patient had used a sample tube of the shampoo, without any ill effects. Patch tests were made with the "Prell" substance, a cleansed portion of the "Prell" metallic tube container, home wave-set lotion, hair lacquer and metal filings from bobby pins. There was a pronounced positive reaction to the "Prell" substance, but reactions to all the other tests were negative. It was considered possible that the patient had come in contact with some irritant at the hospital laboratory where she worked, so she remained at home for ten days, with only a gradual improvement in the dermatitis. Subsequent return to her work produced no exacerbation.

After continued local, soothing therapy and three fractional roentgen ray treatments applied to the scalp and the sides of the face and neck, the eruption gradually subsided and became quiescent in forty days.

181 South Street, Morristown, N J

1 McWhorter, W T. Personal communication to the author.

2 Fishbein, M. Medical Uses of Soap. A Symposium, Philadelphia, J B Lippincott Company, 1945, pp 24 and 161.



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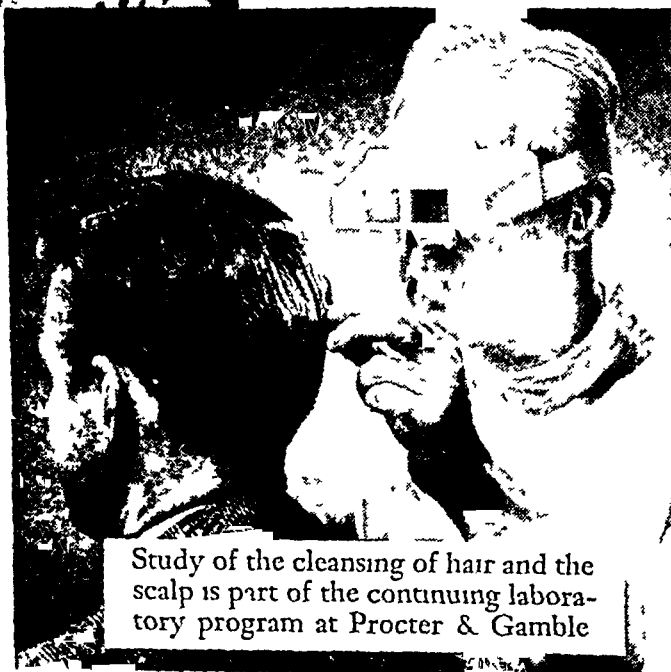
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GEORGE MILLER MACKEL

PORPHYRIC BULLOUS DERMATOSIS

I ZELIGMAN, M D

AND

MAX BAUM, M D

BALTIMORE

PORPHYRIA, a peculiar disease of metabolism in which port-wine-colored urine, containing quantities of uroporphyrin, is excreted, has been reported associated with a number of different clinical manifestations

All normal urine of human beings contains minute quantities of coproporphyrin. Various normal values for the average twenty-four hour excretion of coproporphyrin have been given by authors using different techniques, but the maximal excretion of over 100 specimens previously examined by one of us (I Z) represented 3 micrograms per kilogram of body weight¹. Increased excretion of coproporphyrin, or porphyrinuria, occurs in hepatic diseases, hemopoietic abnormalities and febrile disorders². On the other hand, uroporphyrin is not found in normal urine nor is it specifically found in the aforementioned pathologic states.

Porphyria is characterized by the excretion of the abnormal porphyrin, uroporphyrin, usually in such quantities that the urine is red-dish brown. Many classifications of the porphyrias have been made. Gunther's³ classification has been the one usually accepted and was based principally on the course of the disease: (a) idiopathic acute porphyria, (b) toxic acute porphyria, (c) congenital porphyria and (d) chronic porphyria.

Acute porphyria, whether toxic as the result of excess drug intake or idiopathic has three clinical characteristics: (1) abdominal colic with obstipation and vomiting, (2) dark red urine containing considerable

From the Medical Service of the South Baltimore General Hospital.

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

¹ Zeligman, I. Urinary Excretion of Porphyrin in Dermatoses, *Arch Dermat & Syph* 54:281-291 (Sept) 1946.

² Vannotti, A. *Porphyrine und Porphyrinkrankheiten*. Berlin, Julius Springer 1937.

³ Günther, H. Die Hämatorporphyrie, *Deutsches Arch f klin Med* 105:89-146, 1911.

uroporphyrin during an attack and (3) degeneration of the central and peripheral nervous system, frequently followed by death

Congenital porphyria has been described as a disorder which usually begins in childhood and in which port-wine-colored urine containing large quantities of uroporphyrin are excreted. The porphyrin is deposited especially in bone and teeth, and in about one third of the cases there is an associated hydroa aestivale with bullous lesions occurring on exposure to sunlight and recurring every spring and summer.

Chronic porphyria is a chronic condition characterized by excretion of uroporphyrin accompanied with gastrointestinal symptoms, neurologic or psychiatric abnormalities, photosensitivity or no symptoms at all. Mason, Courville and Ziskind⁴ contended that chronic porphyria was frequently the asymptomatic form of acute or congenital porphyria.

Vannotti's² classification of the porphyrias was as follows: (1) abdominal form, (2) nervous form, (3) cutaneous form and (4) mycoporphyria—cases in which there is excretion of mycoporphyrin.

Brunsting and Mason⁵ expressed the opinion that porphyria may be asymptomatic for years or for life. They contended that all porphyrias were congenital. Some patients might be asymptomatic, but damaging influences, such as alcohol, barbiturates and lead, could result in the clinical expressions of acute, congenital or chronic porphyria. They reasoned that it was therefore probable that some persons have the tendency toward this inborn error of metabolism and that some of these require certain damaging insults to bring out clinical manifestations.

CUTANEOUS LESIONS ASSOCIATED WITH PORPHYRIA

Of the several different dermatologic symptoms and syndromes that may occur with the porphyrias, hydroa aestivale is the commonest. It is a bullous dermatosis in which vesicles and bullae occur only on the parts exposed to solar radiation. It usually starts in childhood and in about one third of the cases is associated with congenital porphyria. The lesions appear on the face, ears, neck and dorsal surfaces of the hands and the forearms and may be followed by crusting, pyogenic infection and atrophic scarring.

4 Mason, V. R., Courville, C., and Ziskind, E. The Porphyrins in Human Disease, *Medicine* **12** 355-439, 1933.

5 Brunsting, L. A., and Mason, H. L. Porphyria with Cutaneous Manifestations, *Proc. Staff Meet., Mayo Clin.* **22** 489-494, 1947.

Though hydroa is the commonest dermatosis associated with porphyria, hyperpigmentation or melanosis sclerodermatous changes and hypertrichosis have occurred with sufficient frequency to be noted⁶

The acquired form of epidermolysis bullosa has also been reported in occasional association with porphyria. This condition is characterized by the formation of vesicles and bullae, followed by crusting, pyogenic infection, atrophic scarring, milia and even atrophy as a result of trauma. Epidermolysis is not a rarity and was noted by a number of medical officers at training centers during World War II. The lesions occur on the feet, hands, knees, elbows, face and elsewhere and may be noted shortly after birth or later in life. There is some dispute whether decrease or absence of elastic tissue is responsible for this condition.

TRAUMATIC CUTANEOUS LESIONS WITH PORPHYRIA

A review of the available literature pertaining to the importance of trauma as a factor in the production of bullae in porphyric persons follows, together with the report of a clinical case.

Arzt and Hausmann⁷ in 1920 described 2 siblings aged 2 and 11, respectively, with hydroa and porphyria. The one 11 years old, whose disease was noted at 5 years of age, had the typical porphyrin spectrum in his urine as well as bullae, crusts and scars on parts exposed to sunlight, particularly during the summer. There was a definite relationship to trauma in some lesions.

In 1925 Gray⁸ described an 18 year old girl who was well until 5 years of age, when blisters appeared on the exposed parts of the body, these lesions recurred each summer. Blisters also appeared on the affected areas as a result of slight injuries. Her reddish urine contained porphyrin. There was also pronounced hirsutism on the face. The liver and spleen were not palpable, and the blood serum gave a positive indirect van den Bergh reaction with $2\frac{1}{2}$ to 3 units of bilirubin.

Marcozzi⁹ found a 10 year old patient with porphyria so sensitive to heat, light pressure and friction that bullae were produced followed by milia. Hypertrichosis was also present.

Meineri⁹ described a 5 year old patient with bullae following trauma and light with sequelae of scars and milia. Hypertrichosis was evident as was pronounced porphyria. He suggested that hydroa lesions

⁶ Turner, W. J., and Obermayer, M. E. Studies on Porphyria. II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, *Arch Dermat & Syph* **37**:549-572 (April) 1938.

⁷ Arzt, L. and Hausmann, W. Zur Kenntnis der Hydroa, *Strahlentherapie* **11**: 444-459 1920.

⁸ Gray, A. M. H. Haematoporphyrin Congenita with Hydroa Vacciniforme and Hirsuties, *Quart J Med* **19**: 389-392 1926.

⁹ Cited by Turner and Obermayer⁶ and by Borda¹².

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In 1925 Gray⁸ described an 18 year old girl who was well until 5 years of age when blisters appeared on the exposed parts of the body, these lesions recurred each summer. Blisters also appeared on the affected areas as a result of slight injuries. Her reddish urine contained porphyrin. There was also pronounced hirsutism on the face. The liver and spleen were not palpable, and the blood serum gave a positive indirect van den Bergh reaction with $2\frac{1}{2}$ to 3 units of bilirubin.

Marcozzi⁹ found a 10 year old patient with porphyria so sensitive to heat, light pressure and friction that bullae were produced followed by milia. Hypertrichosis was also present.

Meineri⁹ described a 5 year old patient with bullae following trauma and light with sequelae of scars and milia. Hypertrichosis was evident as was pronounced porphyria. He suggested that hydroa lesions

⁶ Turner W J, and Obermayer M E. Studies on Porphyria. II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis. *Arch Dermat & Syph* **37** 549-572 (April) 1938.

⁷ Arzt L and Hausmann W. Zur Kenntnis der Hydroa, Strahlentherapie **11** 444-459 1920.

⁸ Gray A M H. Haematoporphyrin Congenita with Hydroa Vacciniforme and Hirsuties. *Quart J Med* **19** 389-392 1926.

⁹ Cited by Turner and Obermayer⁶ and by Borda¹².

do not result directly from the photosensitizing action of porphyrins but that, because of the photodynamic action of these substances, the skin was altered and made more sensitive to trauma following exposure to light

Schreus and Carrie¹⁰ discussed the case of a 30 year old man with porphyria whose disease started at 5 years of age. Typical blisters and scars appeared on the exposed parts especially during the summer. Trauma was also recognized as a factor in the production of the blisters. The result of the galactose tolerance test was normal.

Gottron and Ellinger¹¹ reported the case of a 29 year old man whose eruption began at 7 years of age. Vesicular lesions were found on the exposed parts of the body, especially during the spring and summer. Scarring and even muscular atrophy were present. Considerable porphyrin was found in the urine, but results of tests of hepatic function were normal. Experimentally they found increased sensitivity only with the ultraviolet rays of the Kromayer lamp with pressure, and they therefore reasoned that three factors were necessary for the production of blisters: light, trauma and porphyria.

Cerutti⁹ described the cases of 3 men with porphyria whose symptoms commenced in adult life. They had melanosis, hypertrichosis and bullae on the exposed parts of the body following trauma. He also reported positive Nikolsky signs in his cases. In addition, he cited a case by Radaelli in a 35 year old man with porphyria, in whom bullae appeared on exposed parts of the body following trauma.

In 1938 Turner and Obermayer,⁶ in a classic article with a complete bibliography, described a case of porphyria accompanied with epidermolysis bullosa, hypertrichosis and melanosis in a 29 year old woman whose symptoms started at 20 years of age. Results of histologic study were compatible with epidermolysis bullosa. Experimental attempts to reproduce lesions by trauma and by ultraviolet irradiation were unsuccessful, but uroporphyrin I was isolated from the urine. Lesions reappeared every summer at points of trauma, especially on the hands, elbows and ankles. The liver and spleen were not palpable, and therapeutically there was no response to liver therapy.

Hubner¹² in 1940 reported a group of 7 cases in men aged 47 to 60, with pigmentation, hydroa-aestivale-like vesicles, crusts and scars on the forehead, cheeks, nose, chin and external auricles and with epi-

10 Schreus, H. T. and Carrie, C. Beobachtungen bei einem Fall von kongenitaler Porphyrie, *Dermat. Ztschr.* **62** 347-357, 1931.

11 Gottron, H., and Ellinger, F. Beitrag zur Klinik der Porphyrie, *Arch. f. Dermat. u. Syph.* **164** 11-43, 1931.

12 Hubner, K. Porphyrinuntersuchungen bei einer Gruppe von Dermatosen, *Arch. f. Dermat. u. Syph.* **180** 289-290, 1940.

dermolysis-bullosa-like vesicles and atrophic and pigmented scars on the dorsal surfaces of the hands and fingers. In all 7 patients, evidence of hepatic damage was found by at least one test of hepatic function. The eruption was noted to be worse in spring and summer, while direct evidence of the importance of trauma was shown in 3 cases by experimental production of blisters. Porphyria was observed in all of these cases. He concluded that porphyria may be associated with hydroa vacciniforme and epidermolysis bullosa and to a greater or less extent with hepatic damage.

In 1945 Borda¹³ described 6 cases in adults characterized by bullous and eroded lesions on the exposed portions of the body, hyperpigmentation and porphyria. Bullae followed by erosions and later by pigmentation were the result of exposure to sunlight, cold and trauma. Generalized pigmentation, milia, pyoderma and hypertrichosis also occurred. Reddish urine containing porphyrins was present, but uroporphyrin was not identified. His 6 cases were divided equally between the sexes, and the eruption first appeared from 29 to 58 years of age. One woman was treated with estrogenic hormones, calcium and liver extract without a favorable response.

Brunsting and Mason⁵ called attention to 4 cases of chronic porphyria with cutaneous manifestations occurring in adult life. The 3 male patients and 1 female patient had bullous eruptions on the exposed portions of the body, and some had melanosis, hypertrichosis, milia and/or senile elastosis. Two had a definite family history of latent porphyria. All 4 were chronically alcoholic, and all 4 showed some liver dye retention. Trauma seemed important in at least 2 of the cases. They were unsuccessful in experimental production of the bullae.

Trauma has not been observed to play a part, however, in the production of bullae in some cases of chronic porphyria. Thus Taylor, Solomon, Weiland and Figge¹⁴ reported a case in a 26 year old woman with bullae, crusts and scars on parts exposed to the sun and with generalized abdominal pain. The cutaneous lesions continued throughout the winter, but became worse during the summer. The urine was reddish brown and showed typical spectroscopic bands of coproporphyrin but no reddish fluorescence under Wood's light. Coproporphyrin was found (300 to 1,600 micrograms daily), but the presence of uroporphyrin was indefinite. Evidence of hepatic damage was found by the sulfobromophthalein sodium test, but results of all other tests of hepatic function were normal. Treatment with calcium lactate, sodium

13 Borda I M. Porfiria ampollar y erosiva pigmentada del adulto, *Prensa med argent* 46:2261-2272, 1945

14 Taylor I J, Solomon M L, Weiland, G S, and Figge, F H J. Chronic Porphyria, *J A M A* 131:26-29 (May 4) 1946

bicarbonate, riboflavin, solu B® (a mixture of thiamine hydrochloride, 10 mg , riboflavin, 10 mg , pyridoxine hydrochloride, 5 mg , calcium pantothenate, 50 mg , and nicotinamide, 250 mg , in powder form for injection after proper solution has been effected), crude liver extract and vitamin C were to no avail

REPORT OF A CASE

C H K, 45 year old restaurateur, was first seen in dermatologic consultation by one of us (I Z) July 8, 1947, because of blisters and crusts on the hands, wrists, face and neck of eight months' duration

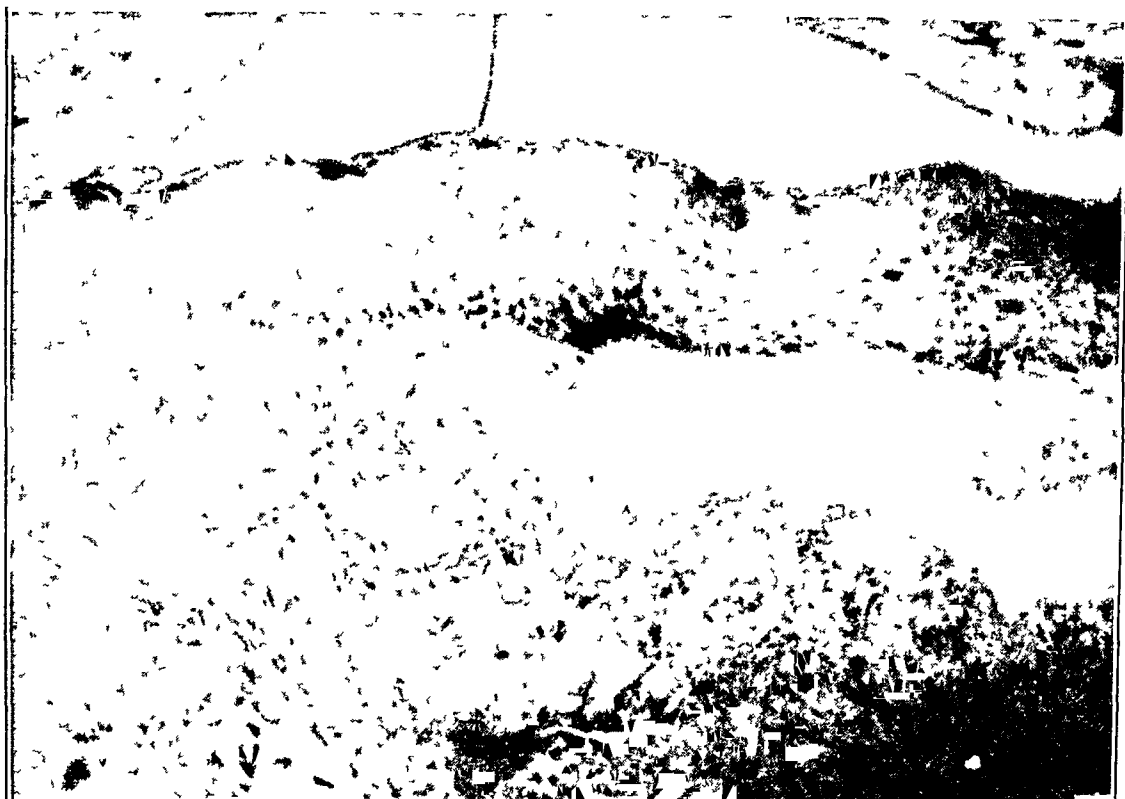


Fig 1—(Weigert's stain) Bullous lesion on the wrist There is a large flaccid bulla containing serum and many red blood cells The roof of the bulla is composed of slightly atrophic intact epidermis The floor of the bulla is composed of moderately edematous collagen with a few fibroblasts and mononuclear cells The elastic tissue fibers appear slightly broader and stain more intensely than normally, but these alterations are within the normal range for the age of the patient and for the area from which the biopsy specimen was obtained (Description from Dr F A Ellis)

The family history was essentially normal His second wife had active pulmonary tuberculosis and had had a thoracoplasty a year previously There was no history of porphyria or a similar dermatosis in any relative

His past history had been essentially normal except for a mental illness which he had had from 1941 to 1945 and from which he had apparently recovered

His respiratory system was normal, and frequent roentgen check-ups for pulmonary tuberculosis had shown no pathologic changes. There was a mild productive cough but no hemoptysis. At times he had had spells of precordial pain, but four electrocardiograms had been normal. The patient's appetite was excellent, and there had been no recent change in weight. For years, he had been unable to tolerate fatty foods, because their ingestion caused pain in the right upper abdominal quadrant. He had noticed pinkish urine at times for the previous several months. There was no pyuria, dysuria, hematuria or renal colic. He denied venereal diseases. There was no paralysis, weakness or paresthesia. During his "nervous breakdown" several years before, he had felt persecuted and hysterical and imagined "all sorts of things," but had had no mental difficulties for the two



Fig. 2—Arrows point to unruptured bullae on the dorsal surfaces of the fingers. There are crusted and eroded lesions as well as atrophic scarring. Amputation of three fingers of the left hand was the result of a previous injury.

years prior to examination. The patient owned a bar and was a heavy drinker. Without alcohol, he felt generally much better. He smoked 1 to 2 packs of cigarettes daily and slept six to eight hours each day.

His present illness started about eight months previously, at which time blisters had appeared on the dorsal surfaces of both hands following trauma. Since then he had had recurrent bullae on the dorsal surfaces of both hands and on the forearms, neck and ears. He had noted that he was worse during the summer, following exposure to the sun. He could produce a blister on the dorsa of his hands within twelve hours after slight trauma. In fact, lesions on the forearms had never been present until the summer when he began to wear short-sleeved shirts. Many of these bullae were followed by crusts, which lasted for weeks and months. At the sites of the bullae, atrophic scarring and depigmentation resulted. He had also noted symmetric red patches on the eyelids and loss of pigment and stiffness on the cheeks and neck.

Physical examination revealed a well nourished, well developed, somewhat obese, fair-complexioned white man. There was no cyanosis, edema or jaundice. His head and neck, except for the skin, were essentially normal. The thorax was symmetric and slightly emphysematous. The chest was clear to auscultation and percussion. His heart was not enlarged to percussion, there were no murmurs, and his pulse rate was equal, normal and regular. His blood pressure was 130 systolic and 96 diastolic. His abdomen was soft, contained no palpable masses or organs and presented no rigidity or tenderness. The extremities were normal except for the skin.

His skin was fair, with considerable freckling, and his hair reddish blonde. There were a few clear half split-pea sized vesicles on the dorsa of the hands and wrists. There was a moderate number of eroded vesicles and bullae and crusted lesions on the dorsa of the hands, wrists, forearms, face, ears and back of the



Fig 3—Crusted and eroded bullous lesions with sclerodermatous changes on the back of the neck.

neck and numerous areas of atrophic scarring. No lesions were present on the feet or ankles. On the cheeks and lateral and posterior cervical areas were symmetric patches of depigmentation and thickened hide-bound skin. On both upper eyelids there were reticulated telangiectasia and erythema.

The hemogram revealed 3,950,000 red blood cells, hemoglobin 85 per cent (145 Gm) and 6,900 white blood cells. The result of the serologic test for syphilis was negative. A routine urinalysis revealed no albumin or sugar, but the urine was pinkish in ordinary light and revealed red fluorescence with Wood's light. The urine was examined on a number of occasions, and each examination revealed red fluorescence with Wood's light, whereas all control specimens were yellowish, green or light blue with Wood's light.

He was treated with crude liver extract, 1 cc intramuscularly, for eight weeks without improvement. He was given various topical medications, such as penicillin ointment for the pyococcic aspect of the crusted lesions, antipruritic ointments,

sun-filtering ointments containing cycloform® (isobutyl paramiobenzoate), and a chlorophyll-containing ointment for the promotion of epithelization—none of which was spectacularly effective. Avoidance of alcohol made him feel much better generally, but did not influence the occurrence of lesions. Treatment with tripeleminamine hydrochloride was tried, but could not be tolerated because of nausea and vomiting. He had, of course, been directed to avoid exposure to the sun and trauma.

Tests with ultraviolet rays revealed no remarkable sensitivity. The biopsy showed a subepidermal bulla, with apparent complete separation of epidermis from the dermis and with both epidermis and dermis intact. Weigert's stain showed alteration of elastic fibers consistent with the age of the patient and the area from which the biopsy specimen was taken. A study of several twenty-four hour specimens of urine revealed an average of 248 micrograms of coproporphyrin, which is within normal levels for his weight (22 micrograms per kilogram). Considerable uroporphyrin was present in the urine, the presence of this abnormal porphyrin established the diagnosis of porphyria. Insufficient cooperation from the patient prevented the pooling of enough urine to obtain adequate amounts of uroporphyrin for isolation. The extraction of both porphyrins and the quantitative measurement of coproporphyrin were performed as described in a previous report¹ (Dr E. H. Macchling, of the Department of Dermatology, Columbia College of Physicians and Surgeons, made the quantitative determination of the coproporphyrin, as adequate facilities for such were unavailable to us at that time). The uroporphyrin bands in 12 per cent ammonium hydroxide were 6,600 to 6,550 angstrom units and 6,200 to 5,940 angstrom units.

On September 10 he was admitted to the South Baltimore General Hospital to the private service of one of us (M. B.) for study. History and physical examination revealed nothing which had not previously been noted and recorded, but further laboratory studies especially directed at hepatic function were emphasized.

The urine was amber, with a specific gravity of 1.017. The results of tests for albumin were negative, for glucose negative and for urobilinogen positive. A complete blood cell count showed 96 per cent hemoglobin, 4,700,000 red blood cells and 8,100 white blood cells, with a differential count of 61 per cent polyphuclear neutrophils, 36 per cent monocytes and 3 per cent band forms. The result of the Kahn test of the blood was negative, the blood sugar was 140 mg per hundred cubic centimeters (two days later 100 mg) and the blood nonprotein nitrogen was 40 mg per hundred cubic centimeters. A series of tests of the gallbladder revealed a poor shadow of the gallbladder, with no evidence of stones. The prothrombin time was eighteen seconds (normal sixteen seconds). The results of the cephalin flocculation test were negative in twenty-four hours and 1 plus in forty-eight hours. The sulobromophthalcin sodium test revealed 36 per cent retained after fifteen minutes and only a trace after thirty minutes. Blood cholesterol was 195 mg per hundred cubic centimeters. Total serum protein was 6 mg per hundred cubic centimeters with albumin 33 mg, globulin 27 mg and an albumin-globulin ratio of 1.2. The results of the van den Bergh test was negative. The icteric index was 1.0 to 1.5.

By late October he began to improve, but he still had some new vesicles following trauma. By December 10 there were no further active lesions. Later during the winter, he had no active bullae but complained mainly of the stiffness of the neck and cheeks associated with the sclerodermatous changes. The urine at this time was still pinkish and still showed red fluorescence.

COMMENT

No attempt is being made in this paper to discuss the chemical, physiologic or metabolic aspects of the porphyrins. For these, the reader is referred to several excellent monographs on the subject.¹⁵ Suffice it to say that coproporphyrin is normally excreted in the urine in minute quantities. Increased excretion of urinary coproporphyrin, called porphyrinuria, occurs with febrile diseases, hepatic disorders and hemopoietic abnormalities,² while a previous study by one of us¹ failed to show any significant increase in urinary excretion of coproporphyrin in many dermatoses, including those believed to be caused or exacerbated by light. The only dermatosis which was associated consistently with porphyrinuria was acute disseminate lupus erythematosus, but this is easily explained by the accompanying hyperpyrexia. No uroporphyrin was observed in that series.

The patient described in this paper was referred to us because of blisters at sites of trauma. The history and the lesions themselves were consistent with acquired epidermolysis bullosa, but because the feet were not involved, because the lesions were present on the exposed portions of the body only and because there was an exacerbation during the summer, with an extension of the lesions up the forearms associated with the wearing of short-sleeved shirts, the possibility of porphyria was considered. When questioned about the color of his urine the patient replied that his wife had called his attention to a pinkish red discoloration a few months previously. A spot specimen of urine was thereupon examined and definitely was pinkish. When visualized with Wood's light, there was very evident reddish fluorescence. On his next visit he brought a twenty-four hour specimen which also had the pinkness and the red fluorescence, a persistent observation in all subsequent examinations. The urinary excretion of coproporphyrin was within normal limits, but the abnormal uroporphyrin was present. Unfortunately, no standards were available for an estimation of its excretion in a twenty-four hour specimen. The presence of uroporphyrin, however, definitely established this as a case of porphyria, since uroporphyrin is not found in normal urine.

The most frequent dermatosis accompanying porphyria is hydroa aestivale, characterized by vesicles and bullae followed by crusting and atrophic scarring on those parts of the skin exposed to solar radiation. This condition commonly starts in childhood, and in some cases trauma has been noted as a factor in the production of the lesions.

15 Vannotti,² Mason, Courville and Ziskind,⁴ Dobriner, K., and Rhoads, C. P. The Porphyrins in Health and Disease, *Physiol Rev* 20 416-468 1940

Hyperpigmentation and hypertrichosis have been not infrequently noted in conjunction with porphyria, but these were not present in this instance. On the other hand, scleroderma, which may occur as a sequel in some cases, was present on the face and especially the neck. In fact during the winter months the patient's chief complaint was stiffness of the neck.

Epidermolysis bullosa has been noted with some cases of porphyria and was considered as a possibility in this instance. A study of reported cases and our own reveals, however, that when porphyria is a factor in trauma-produced bullae, the lesions occur only on those parts of the skin exposed to sunlight. Our patient traumatized his skin lightly for us on exposed and nonexposed parts, with the subsequent formation, twelve hours later, of bullae only on the parts exposed to sunlight. Furthermore, his condition was exacerbated during the summer and the eruption receded during the winter. Therefore, we concluded that three factors were necessary for the production of this syndrome: porphyria, sunlight and trauma. We believe that in all cases of suspected epidermolysis bullosa, especially of the acquired type which is limited to the exposed portions of the body, the possibility of porphyria must be considered. We do not believe, however, that all cases of hydroa or epidermolysis occur in association with porphyria.

Many authors have considered hepatic damage as an important factor in the porphyrias, and some have found evidence for this hypothesis. Our patient was hospitalized with this in mind and despite various tests hepatic function was found to be within normal limits. If hepatic damage is present possibly the liver reserve of our patient was such that none of the tests revealed dysfunction.

We are inclined to agree with Brunsting and Mason⁵ that some persons congenitally have the tendency to this inborn error of metabolism and that some require certain damaging insults to bring out clinical symptoms. As in their cases, our patient also was chronically alcoholic and alcohol undoubtedly played a major precipitating role. Others have reported barbiturates, lead and other chemicals as precipitating factors.

Chronic porphyria, as exemplified by our case, may be associated with neuropsychiatric and gastrointestinal symptoms as well as cutaneous ones. Whether the psychosis which had required the patient's institutionalization was associated with the porphyria is difficult to evaluate in view of the failure of any one at that time to take notice of the coloration of his urine. A similar indecisive conclusion must be taken of his gallbladder colicky complaints similar to those reported in acute and chronic porphyria.

In most cases of porphyria and/or hydroa aestivale there is no increased erythematous sensitivity to light nor can one usually experi-

mentally produce lesions with sunlight or selected wavelengths of ultraviolet rays. Our case was no exception in this respect, at least insofar as sensitivity to mercury vapor ultraviolet rays was concerned. A carbon arc source of ultraviolet rays would be more appropriate for cases of porphyria, but such a source was unavailable to us.

Meineri⁹ was the first to suggest that hydroa lesions do not result directly from the photosensitizing action of porphyrins but that, because of the photodynamic action of these substances, the skin is altered and made more sensitive to trauma after exposure to light. Gottron and Ellinger,¹¹ in a case of porphyria, experimentally found increased sensitivity only to the ultraviolet rays of the Kromayer lamp with pressure, and they therefore reasoned that three factors were necessary for the production of the blisters: light, trauma and porphyria. Hubner,¹² in 7 cases of porphyria with blisters on exposed portions of the body, was able experimentally to produce blisters traumatically in 3 cases. Blum and Pace,¹⁶ in discussing the failure of experimental photosensitization to porphyrins, hypothesized that hydroa lesions result from trauma rather than from light.

As a result of a review of the literature and observations in our case, we also believe that the blisters present in porphyrias, whether they have hitherto been called hydroa aestivale or epidermolysis bullosa, are all essentially the same and are the result of some change in the skin due to the presence of the photodynamic uroporphyrin which makes it more susceptible to a combination of light and trauma. Thus porphyria, sunlight and trauma are all necessary factors in the production of the bullae. It is therefore our opinion that "porphyric bullous dermatosis" is the best inclusive term for this condition, since the porphyria is the essential biochemical basis for this clinical entity.

SUMMARY

The bullous eruptions that occur with porphyrias are reviewed with special emphasis on the factor of trauma. A case is reported in a chronically alcoholic patient with chronic porphyria in whom trauma was a factor in producing bullae on the skin exposed to sunlight.

As a result of a review of the literature and our own case study, we believe that the bullous eruptions present in porphyric patients, whether hitherto named hydroa aestivale or epidermolysis bullosa, are essentially the same and are the result of some change in the skin due to the presence of the photodynamic uroporphyrin which makes it more susceptible to light and/or trauma. By no means, however, are all cases

16 Blum, H. F., and Pace, N. Studies of Photosensitization by Porphyrins. *Brit J Dermat* 49: 465-487, 1937.

of hydroa or epidermolysis of porphyric causation. We propose the use of the term "porphyric bullous dermatosis" for the disease in such cases.

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ABSTRACT OF DISCUSSION

DR LOUIS A BRUNSTING, Rochester, Minn. This is an excellent presentation of a difficult subject. The distinctive feature of porphyria is that abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces, but there is some argument as to whether the particular isomer of porphyrin that is excreted is exactly the basis for definition of the classification of the type of porphyria that is present. Porphyria is a rare familial metabolic fault with various forms of clinical expression, persons with the disease may be asymptomatic for years or for life, and often the urine does not have a port wine color even when it contains abnormal porphyrins. Surveys of families in which this inborn error of metabolism occurs may disclose the presence of uroporphyrin or the colorless porphobilinogen in the urine of apparently normal persons. Tests for porphyrins, at least qualitative tests, are not beyond the range of most hospital facilities, for no elaborate equipment is required.

In acute porphyria, pigmentation occurs, and sometimes solar urticaria, but other cutaneous reactions are infrequent, in congenital porphyria, the outstanding change is the hydroa-like reaction of the light-exposed surfaces of the skin as well as erythrodontia. Bullous eruptions occur in the adult with chronic porphyria (often as the presenting symptom), as in the case under discussion, which I like to consider an example of the tardive form of congenital porphyria. Such cases are probably commoner than is generally supposed. Under the influence of light and of minor trauma, lesions similar to those seen in epidermolysis bullosa develop in the exposed skin. The latter condition represents a hereditary fault in the binding mechanism of the skin, but no actual relationship between true epidermolysis bullosa and porphyria has been established. Other changes which occur regionally in the skin in chronic porphyria are pigmentation, hirsutism, milia and an alteration in texture which resembles scleroderma. Microscopically, such skin shows the picture of senile elastosis, particularly in regard to the peculiar staining reaction of the collagen.

Little is known concerning the factors which may precipitate the manifest syndrome of porphyria or which may influence its course one way or another. In certain cases, a damaging influence on the liver, either by disease, such as cirrhosis, or by hepatotoxic drugs or poisons (alcohol, barbiturates, arsenic, lead) appears to contribute to the development of obvious symptoms of porphyria. Within a comparatively short period of time, I have observed 5 patients with chronic porphyric bullous dermatosis as described herein, in each instance a history of chronic alcoholism and evidence of hepatic dysfunction were present, and it seemed reasonable to relate these factors to the precipitation of the clinical syndrome. It has been claimed that three factors are necessary for the production of blisters: light, trauma and porphyria. However, this does not explain the absence of symptoms in cases of latent porphyria even when there are large amounts of uroporphyrin in the urine. I would offer an added factor for consideration, that is damage to the liver, perhaps of a degree unmeasurable by current tests of hepatic function. The exact mechanism is unknown. Perhaps the damaged liver influences the

enzyme system of the skin, which, in the presence of porphyria, affects the binding qualities of the connective tissue in the regions that are exposed to light. In my experience, the general health of these patients improves and the cutaneous symptoms subside under an anticirrhotic regimen.

DR GEORGE H. CURTIS, Cleveland. I had the opportunity to observe briefly a case which I consider similar to that of Drs. Zeligman and Baum. The patient was a white laborer, aged 49, whom I saw in July 1947. The disease had its onset in May 1946, and in the early stages he found it practical to keep his sleeves down to prevent lesions on the forearms. The face, neck, ears and hands were sites of itching papules and blisters, which were more numerous and severe in summer. In the winter the face and neck were free of lesions, but bullae continued on the hands. The family history and general physical examination elicited no unusual observations. The face, neck and hands were deeply tanned, and the skin of the neck was considerably weatherbeaten. There was also lichenification. Excoriations, several small denuded lesions and urticaria-like maculopapules were present. A single pea-sized bleb was located on the nape of the neck. Bullae, scars and milium-like lesions in old atrophic scars were evident on the fingers and knuckles.

The results of the routine hemogram, urinalysis and blood sugar test were within normal limits. The observations of histologic examination of a bulla excised from the hands were considered consistent with those of epidermolysis bullosa. On two successive days the urine was qualitatively examined for porphyrins, with positive results; unfortunately, the porphyrins were not identified. Attempts to produce lesions with the Kromayer lamp and by compression with a quartz filter were unsuccessful. Six hours after pinching the dorsum of the left hand a bulla appeared at the site. However, no bullae appeared on the forearms or neck where tested. In October 1947 the patient exhibited improvement of the face and neck, but bullae remained on the hands. A twenty-four hour urine specimen at this time showed no porphyrins. The patient has since been inaccessible for observation. The number of cases of this syndrome seems to be increasing. After studying the literature, I believe that identification depends on the establishment of routine laboratory procedures for at least the qualitative identification of porphyrins.

Clinical observation leaves no doubt that certain dermatoses are produced by the photosensitizing effect of sunlight as exemplified by urticaria solare and hydro-aestivale without porphyrinuria. The role of porphyrins in photosensitivity of the skin is equivocal. Hematoporphyrin and some of the naturally occurring porphyrins are known to induce photosensitivity. The porphyrins are deposited in the tissues and have been found high in the papillae of the dermis. Thus the conditions sunlight, porphyrinuria and fixation of porphyrins in tissue are simultaneously present for the development of photosensitivity and the production of the lesions of hydroa aestivale and the epidermolysis-bullosa-like dermatoses. On the whole, however, experimental attempts to reproduce the lesions by artificial light, as well as controlled sunlight, have not been successful. Blum and Pace (*Studies of Photosensitization by Porphyrins*, *Brit J Dermat* 49:465-485 [Nov] 1937) observed vesiculation at the sites of subepidermal injection of hematoporphyrin in a normal subject following exposure to sunlight nine weeks later. However, hematoporphyrin does not occur as such in disease in human beings.

It is also difficult to evaluate trauma in the production of lesions in the porphyrin-sunlight-trauma complex. In the case of Drs. Zeligman and Baum, and in mine bullae were produced by slight trauma only on the exposed skin. In Meineri's case, cited by the authors, bullae appeared only after trauma, even

though the patient's skin was deeply pigmented on prolonged exposure to sunlight. Nevertheless, bullae may be produced by pressure with a Kromayer lamp and quartz filter in a normal person. Bullae have been reported to occur only on the feet, the quantity more numerous in summer, in a case of porphyrinuria with epidermolysis bullosa. Trauma is followed by bullae in the absence of sunlight and porphyrinuria in epidermolysis bullosa.

During the summer months there is a certain amount of swelling and edema of the dependent parts of both upper and lower extremities and traumatic blistering occurs more readily than in cooler seasons. Among other factors I believe that the borderline normopathologic state of the vascular bed in the dermis plays some part in the increase of symptoms in epidermolysis bullosa with or without porphyrinuria. One wonders whether the porphyrins are as important as genetics, sunlight, trauma and other factors in the production of lesions in hydroa aestivale and epidermolysis bullosa.

DR ISRAEL ZELIGMAN, Baltimore. Our purpose in presenting this paper was twofold. We wished to stimulate and restimulate interest in the porphyrins and the porphyrias in their relationship to the dermatoses, secondly, we wished to call attention to the possible importance of porphyria in the acquired and possibly in the congenital types of epidermolysis bullosa. We think that every case of epidermolysis bullosa should be studied in this direction.

EOSINOPHILIC GRANULOMA

With Simultaneous Involvement of Skin and Bones

JAMES H. McCREARY, M.D.

COLUMBUS, OHIO

EOSINOPHILIC granuloma of the bone has been established as a disease entity by Otani and Ehrlich¹ and by Lichtenstein and Jaffe,² in 1940. The eosinophilic granulomas of the skin as reported in the literature have recently been reviewed by Weidman,³ Lewis and Cormia,⁴ Lever⁵ and Dobes and Weidman.⁶ The cutaneous manifestations of eosinophilic granuloma have varied so widely in their clinical and histopathologic features that the disease is not yet considered as a disease entity.

REPORT OF A CASE

V. M.,⁷ an 11 year old white girl, was first seen at the University of Chicago Clinics on Jan 9, 1947. She complained of tender tumefactions and ulcerations of the skin on the upper part of the chest and scalp. She had been well until the age of 2 years, when she became ill with measles and mumps at the same time. During this illness adenitis of the right submaxillary gland developed, which failed to resolve, and then an ulcer formed. Abscesses of nearby nodes developed and followed a similar course. Since that time the patient has been almost continuously sick, with swelling and ulceration of lymph nodes on the head, neck and thorax. The appearance of each new lesion has been accompanied with a temperature of

From the Section of Dermatology, University of Chicago (Chief of Service, Dr. Stephen Rothman).

1 Otani, S., and Ehrlich, J. C. Solitary Granuloma of Bone Simulating Primary Neoplasm, *Am J Path* **16** 479, 1940.

2 Lichtenstein, L., and Jaffe, H. L. Eosinophilic Granuloma of Bone, with Report of a Case, *Am J Path* **16** 595, 1940.

3 Weidman, F. D. The "Eosinophilic Granulomas" of the Skin, *Arch Dermat & Syph* **55** 155 (Feb) 1947.

4 Lewis, G. M., and Cormia, F. E. Eosinophilic Granuloma, *Arch Dermat & Syph* **55** 176 (Feb) 1947.

5 Lever, W. F. Eosinophilic Granuloma of the Skin, *Arch Dermat & Syph* **55** 194 (Feb) 1947.

6 Dobes, W. L., and Weidman, F. D. Granulomatous Hodgkin's Disease of the Skin with Extreme Eosinophilia, *Arch Dermat & Syph* **55** 212 (Feb) 1947.

7 The patient was presented before the Chicago Dermatological Society on Feb 19, 1947. At that time studies of the case were incomplete. The presentation of this case has been made possible through Dr. Mila Pierce of the Pediatric Department of the University of Chicago Clinics who has been responsible for the medical care of the patient.

99 to 104 F and locally by pain, tenderness and erythema. After rupture of the abscess, the systemic symptoms disappeared. There was a tendency toward slow healing with granulation and scar formation. Following an operation three years previously, in 1944, for the removal of a group of cervical glands, the motion of the shoulders and neck has been restricted because of pain. Roentgen therapy seemed to accelerate healing, with remissions of the symptoms for as long as a year. The total roentgen dosage given to each lesion varied with the depth and extent of the lesion and was between 90 and 660 r. Penicillin and the sulfonamide drugs had no effect on the course of the disease. The disease had been diagnosed at one time as tuberculosis by smear examination and at another time as Hodgkin's disease by lymph node examination.

On examination, the patient appeared to be slightly undernourished. She was afebrile and not acutely ill. Both shoulders were carried forward and elevated.



Fig 1—*A*, clinical photograph of eosinophilic granuloma, showing the unruptured abscesses in the right axilla and some irregular ulcerations of the left upper part of the thorax. *B*, irregular deep ulceration and scarring of eosinophilic granulomas of the neck and back. The abscesses appeared in regions where large lymph nodes are not usually seen.

There was moderate scoliosis toward the right, with moderate reduction of movement to the left hemithorax. A firm spleen was palpable. The liver was felt at the costal margin. The enlarged cervical nodes showed a tendency to mat together. The ulcers of the overlying skin were from 2 to 5 cm in diameter and had soft undermining irregularly shaped edges and irregular granulating bases well vascularized. Some of the ulcers appeared in regions where large lymph nodes are not usually present. The results of the rest of the physical examination were essentially normal (fig 1).

The roentgenogram of the skull revealed an irregular oval dehiscence about 2 cm in diameter, in the right parietal bone under one of the tender swellings. All other bones were normal, including the ribs under the cutaneous ulcerations (fig 2).

Culture of the exudate on blood agar and Sabouraud's mediums showed *Staphylococcus albus*. Acid-fast stains were repeatedly negative. Blood culture and repeated animal inoculations into rats and guinea pigs were negative. Reactions to a tuberculin patch test and blastomycin, histoplasmin and purified protein derivative tests were all negative. Reactions to Kahn tests were negative. A sternal puncture showed the myeloid-erythroblast ratio to be elevated. The sedimentation rate varied between 6 and 41 mm. The white blood cell counts were 8,000 to 25,000, hemoglobin was 11.5 to 14.5 Gm., the red blood cell counts were 3,800,000 to 5,200,000. The differential count revealed polymorphonuclear cells

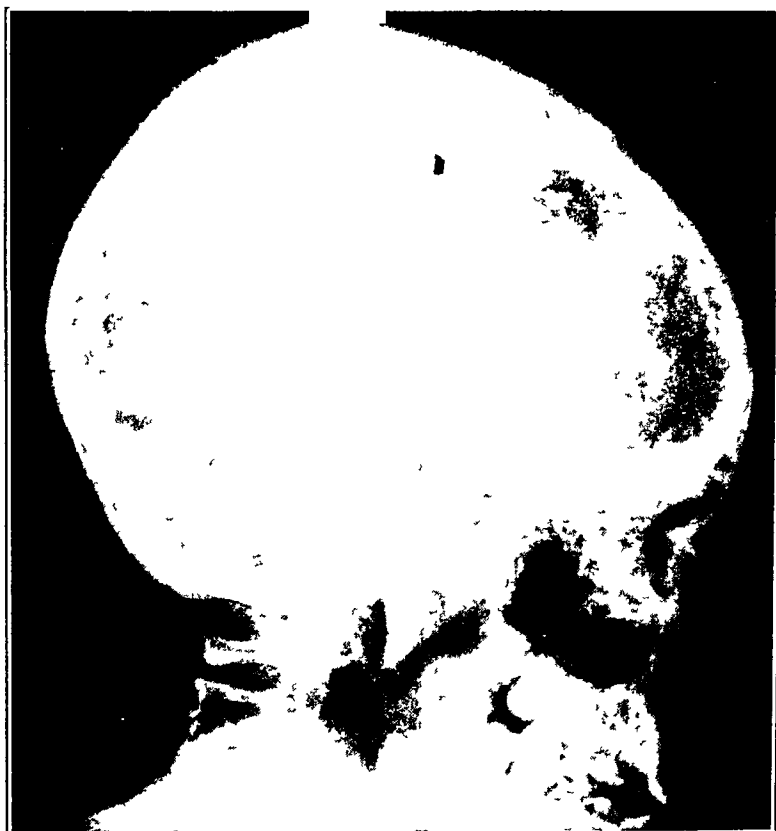


Fig. 2—Roentgenologic examination of the skull, demonstrating an irregular dehiscence of eosinophilic granuloma in the right parietal bone (arrow). The rest of the skeleton showed no evident abnormality.

72 per cent, lymphocytes 26 per cent and eosinophils 2 per cent. Hematocrit was 41. The urine was normal. Serum lipids were normal.

An axillary lymph node removed on January 30 was a large moderately firm node, red-brown and mottled with small lighter (tan) areas. The microscopic sections showed an extensive obliteration of the normal architecture, although small remnants of cortical follicles and cords filled with lymphocytes remained. Sheets of large acidophilic or pale nonfoamy macrophages seemed to have filled in the sinuses as well as the parenchyma. Scattered in great abundance between them were eosinophils and lymphocytes. Some cells with dark nuclei looked like normoblasts. The histiocytes or macrophages frequently had lobulated nuclei, and some

were multinucleated. Neither in their cytoplasm nor in their nuclear form did they resemble Reed-Sternberg cells. There was fibrous thickening of the capsule and decided fibrosis of some of the cell-filled lymphatic sinuses. Fibrous tissue was especially dense around the blood vessels of the hilar portion of the node. Evident in Mallory stain was the presence of clefts or small vacuoles of the cytoplasm of the large macrophages. However, the appearance was different from that seen in the large cells of Gaucher's disease, Niemann-Pick or Hand-Schuller-Christian xanthomatosis. Stains for gram-positive and acid-fast bacteria were negative. Sudan stain revealed an occasional macrophage containing lipid and, in addition, a small amount of lipid material in the fibrous septums. A small amount of this lipid was anisotropic (fig 3 and 4).

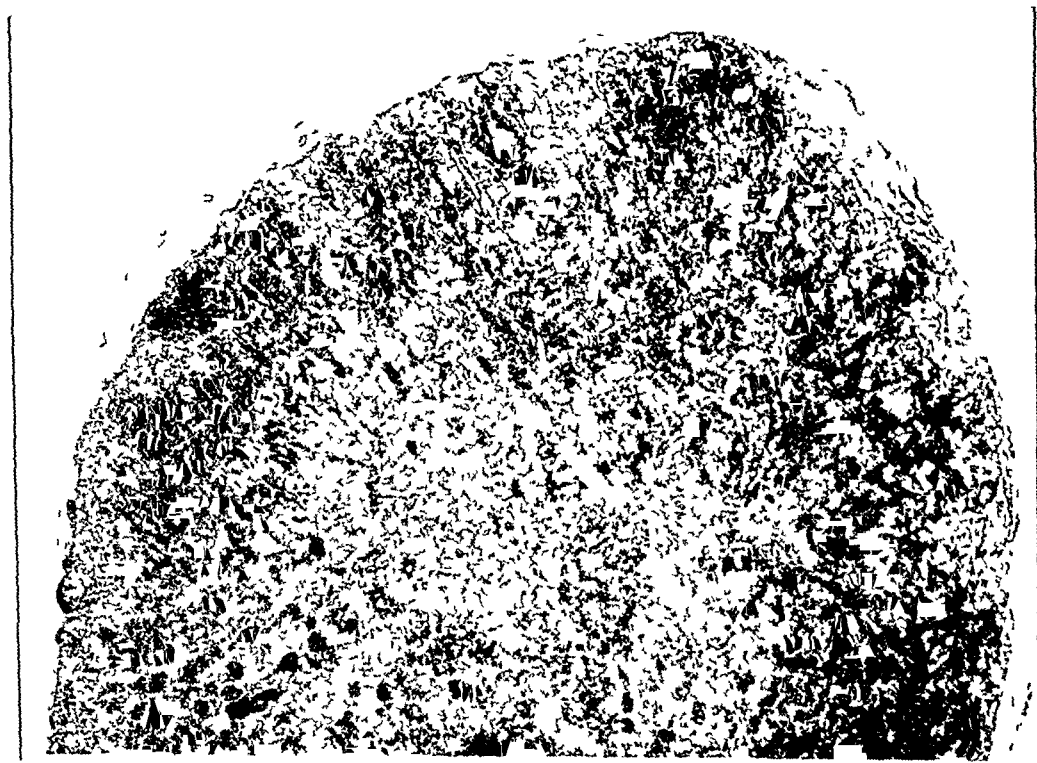


Fig 3—Eosinophilic granuloma. Section from an axillary lymph node (hematoxylin and eosin $\times 11$), showing the extensive obliteration of the normal architecture of the node.

Histologic section of granulation tissue from a sinus revealed many eosinophils, large mononuclear cells with acidophilic protoplasm and lipid content, a few lymphocytes and necrotic debris (fig 5).

The lesion of the right parietal bone was curetted out completely and found to be located immediately beneath the galea and extending down to the inner table, which was intact. The lesion consisted of a mass of brownish granulation tissue. The outer table of bone was padded and eroded. Microscopic study of the granulating mass showed large acidophilic and nonfoamy macrophages with large irregular-shaped nuclei, indistinct nucleoli and moderate amount of cytoplasm. Many of these macrophages were binucleated, and there was some infolding of the nuclear membrane. Scattered among these cells were a moderate number of eosinophils and a few lymphocytes. There were a few multinucleated giant cells, some of these containing vacuoles or slitlike spaces. A stain for fat (sudan IV)

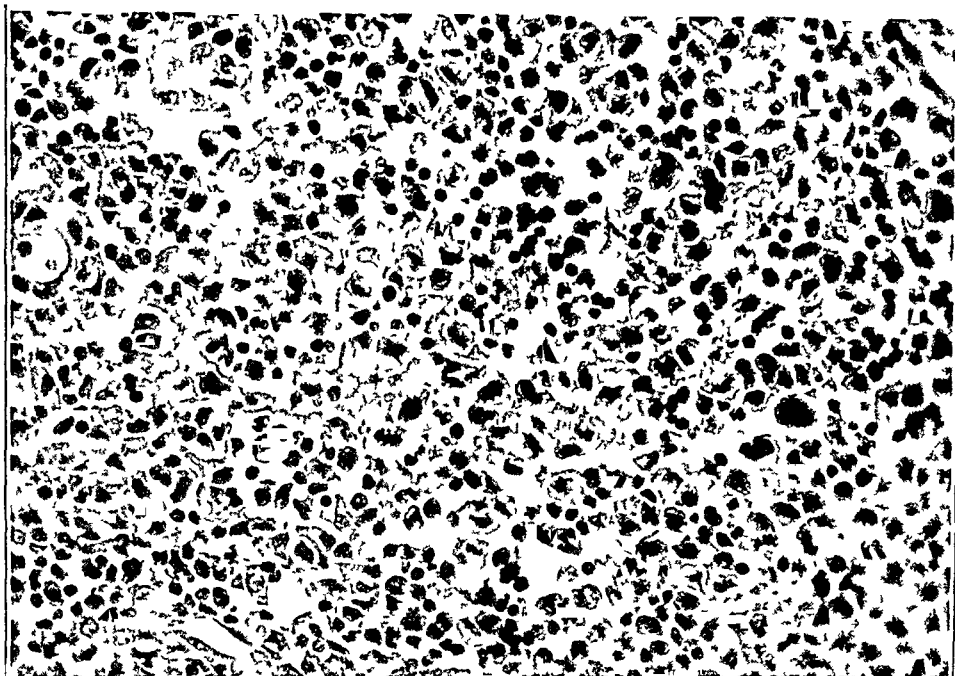


Fig 4—Section of axillary node at higher magnification (hematoxylin and eosin $\times 480$), demonstrating large macrophages or histiocytes. Many of the macrophages are multinucleated. Eosinophils and lymphocytes are scattered among the histiocytes.

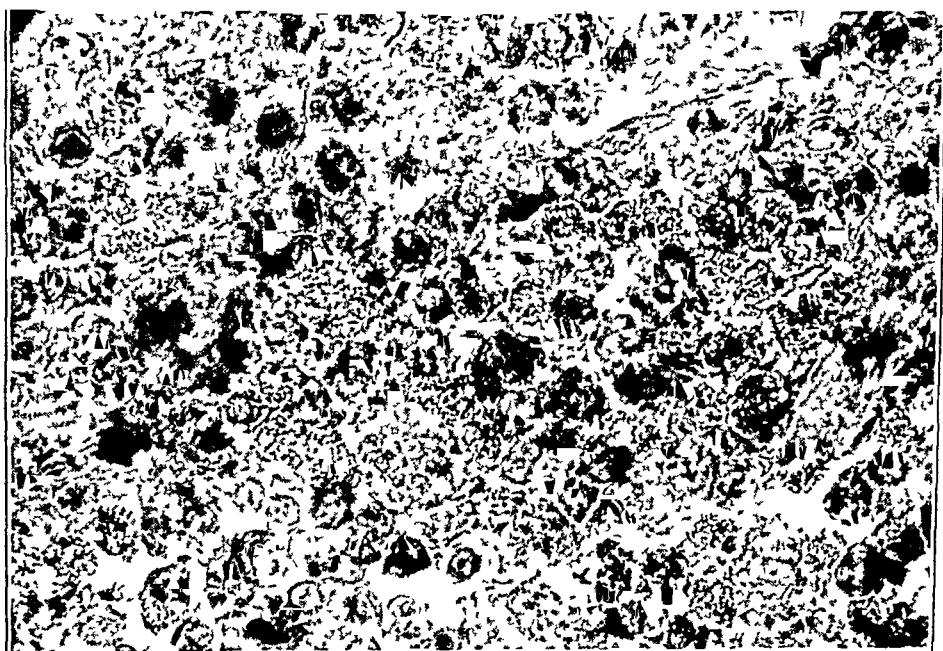


Fig 5—Eosinophilic granuloma. Section from the lesion in the right parietal bone (sudan IV stain $\times 950$), showing the lipoprotein granules in the numerous macrophages. Most of the lipoprotein granules were not anisotropic.

revealed that a moderate number of the macrophages contained fat droplets, or lipoprotein granules, most of which were not anisotropic.

Study of the microscopic sections of the cutaneous lesions showed a thinned out epidermis with a shortening of the rete pegs on the border of the ulcer. There was a decided inflammatory infiltrate in the dermis consisting of macrophages, plasma cells, lymphocytes, eosinophils and polymorphonuclear neutrophils. Beneath the dermis there were sheets of reticulum-like cells with a moderate amount of faintly acidophilic cytoplasm, blurred cell outlines, large and pale nuclei and a faint chromatin network. The nuclei were irregularly shaped, and many of them were indented. Inflammatory cells were scattered among the sheets or reticulum cells, and a few foreign body giant cells were seen. In some of the pieces there were many capillaries (fig 6).

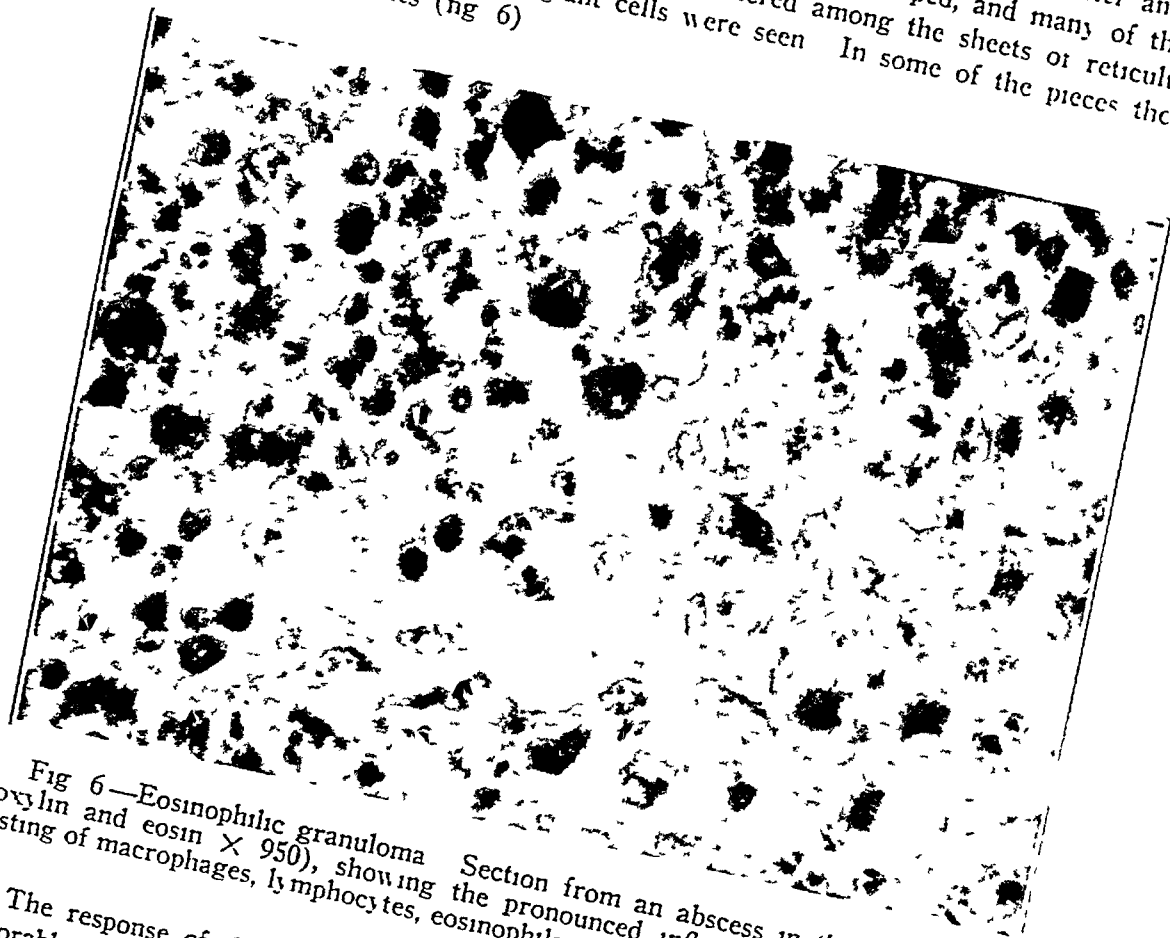


Fig 6—Eosinophilic granuloma. Section from an abscess in the skin (hematoxylin and eosin $\times 950$), showing the pronounced inflammatory infiltrate consisting of macrophages, lymphocytes, eosinophils and polymorphonuclear neutrophils.

The response of the cutaneous lesions to high voltage roentgen therapy was favorable. Each lesion received at least 500 r, and some received as much as 1800 r in fractionated doses (130 kilovolts, 50 cm focus-skin distance, 20 milliamperes, 0 filter and 0.25 half-value layer). After each course of roentgen therapy, the lesions were improved considerably or healed entirely. However, new ones would develop during the course of roentgen therapy. Injections of radioactive phosphorus (P-32) were started later. A total of 2,200 microcuries were given intravenously in two courses, with a daily dosage of 200 to 300 microcuries. For a few days during the last course, the lesions seemed to be aggravated. They drained considerably, and new lesions developed. The temperature increased temporarily to 40.2 C (104.4 F). Beta hemolytic streptococci were cultured from the draining sinuses on several occasions during this episode. The patient was given sulfadiazine by mouth, penicillin parenterally and an aluminum oxide paste.

After this setback, the patient improved rapidly and was discharged Jan 8, 1948. The granulomas showed healing with granulation and scarring. The therapy in the hospital included ultraviolet irradiation to the whole body, supplementary vitamins and physical therapy to the shoulder girdle. It is too early to determine what effect the radioactive phosphorus may have had on the course of the disease.

COMMENT

This is the second case reported in which cutaneous manifestations accompanied a granuloma in the bone. The first case of this kind, with simultaneous but independent involvement of skin and bone, was reported by Curtis and Cawley⁸ in June 1947.

The disease in my case had been diagnosed previously as cutaneous tuberculosis from a smear, yet in this department all animal inoculations, smears and reactions to tuberculin tests were negative. The results of examination of microscopic sections did not favor a diagnosis of tuberculosis, and it is difficult to imagine that the eosinophilic reaction could be masking an underlying tuberculous process. A few giant cells were present, but these were identified as foreign body type. The chest was clear, and no other tuberculous focus could be found.

The disease had also been diagnosed at one time as Hodgkin's disease. The sections of the present review certainly do not show Sternberg-Reed cells or other characteristic features of Hodgkin's disease. It has been emphasized by Weidman³ that "an inter-current eosinophilous disease or at least pathologic substrate can modify or obscure an otherwise readily diagnosable entity," and a masking of Hodgkin's disease should be perhaps considered in this case. The clinical course, however, with the onset in a 2 year old girl and slow progression over a twelve year period, does not suggest Hodgkin's disease at all.

Because of the presence of lipid deposited in moderate amount in macrophages of the sinus tract and of the granuloma of the bone, this condition may be allied with the lipoidoses. Some of the lipid granules were anisotropic, but the majority were not. Foam cells, typical of the xanthomas, were not frequently seen.

Microscopically, the picture resembled most closely the picture seen in the eosinophilic granuloma of bone as described by Lichtenstein and Jaffe²—soft brownish granulation tissue which presented on microscopic section sheetlike collections of large phagocytic cells of the nature of histiocytes, with a moderate amount of cytoplasm, many of them binucleated, presence of a moderate number of eosinophils, and multinucleated giant cells which contained vacuoles or slitlike spaces and, in some instances, sudanophilic droplets. In the case reported, not

8 Curtis, A. C. and Cawley, E. P. Eosinophilic Granuloma of the Bone with Cutaneous Manifestations, *Arch Dermat & Syph* 55:810 (June) 1947.

only did the bone lesion present this picture but also the same eosinophilic granulomatous process was evident in the lesions of the skin. The appearance of the macrophages was different from that seen in the large cells of Gaucher's, Niemann-Pick or Hand-Schuller-Christian disease.

Clinically, my patient had a protracted course. She had never been critically ill. Letterer-Siwe disease makes its appearance mainly in infants and in children below the age of 2 and usually runs an acute or subacute course fatal within a matter of weeks or months.² The soft tissues as the lymph nodes, the tonsils, the thymus, the spleen, the bone marrow, the liver, the lymphoid tissue of the alimentary tract and the skin may show histiocytosis in Letterer-Siwe disease. Only the lymph nodes in this case showed significant enlargement. Although the disease was noted shortly after both measles and mumps, the patient's temperature remained normal except for elevations when new lesions first appeared. Purpura and eczematoid dermatitis, rather characteristic for Letterer-Siwe disease, were absent in this case. The abscessed lymph nodes showed considerable eosinophilia, which ordinarily is not found in Letterer-Siwe disease. The peripheral blood did show mild hypochromic anemia at times, whereas such anemia is steadily progressive in Letterer-Siwe disease.

As of the time of reporting, neither diabetes insipidus nor exophthalmos had developed in the patient. Examination showed that the involvement of the skull bones had not been extensive enough to include the sphenoid and the bones delimiting the orbit. Classic Hand-Schuller-Christian disease certainly can be excluded on the basis that diabetes insipidus and exophthalmos had not developed, and thus the triad of exophthalmos, diabetes insipidus and calvarial defect was far from being complete.

Isolated eosinophilic granuloma of the skin with no involvement of bones and internal organs was reported by several authors. Lewis and Cormia,⁴ Lever⁵ and Buley⁹ have extensively reviewed the American and European literature describing these cases. The clinical appearance of these lesions has greatly differed from those reported by Curtis and by me, insofar as the isolated cutaneous lesions have been described heretofore as benign indolent nonulcerating nodules or plaques, red or purplish, sometimes with a yellowish tinge, sharply margined and located about the head or over the joints. In addition, the isolated benign cutaneous lesions have not been accompanied with lymphadenopathy, and some of them have proved to be radioresistant.

⁹ Buley, H. M. Eosinophil Granuloma of Skin. *J. Invest. Dermat.* **7**: 291 (Dec.) 1946.

Although microscopically the features of cutaneous "benign" eosinophilic granulomas are comparable to that of my case, in the latter there was more phagocytic activity than in the cases reported in the other group. The analysis leads to the conclusions that benign nonprogressive eosinophilic granuloma of the skin is an entity different from the condition in the case reported by Curtis and by me.

SUMMARY

A case with calvarial bone defect and with cutaneous ulcerations is reviewed. The cutaneous ulcers originated partly in the skin proper, and developed partly over abscessed lymph nodes with draining sinuses. Histologically, eosinophils and histiocytic macrophages were the prominent features. Unusual features of this case are onset in a 2 year old girl, protracted course over eleven years, simultaneous presence of cutaneous and bony lesions in different regions, lymphadenopathy and radiosensitivity of the lesions. The differential diagnosis of Hodgkin's disease, eosinophilic granuloma of the bone, eosinophilic granuloma of the skin, Letterer-Siwe disease and Hand-Schuller-Christian disease is discussed.

The lesions in the case reported showed remarkably good response to bone curettage, local roentgen irradiation and intravenous radioactive phosphorus (P-32) therapy.

The case reported closely resembles that of Curtis. The histologic features in both these cases were similar to those of benign isolated eosinophilic granuloma of the skin. However, they definitely differed from the features in cases of benign disease representing systemic disease with bone and soft tissue destruction, and it is assumed that the two groups of diseases represent different entities.

ADDENDUM

After completion of this manuscript the patient was again seen in this department. There had been a recent flare-up in two lesions, and a new lesion had developed on the left upper arm.

Dr Eleanor M. Humphreys of the Pathology Department and Dr Stephen Rothman of the Dermatology Section, University of Chicago Clinics, gave advice in the preparation of the manuscript.

CUTANEOUS DIPHTHERIA

Observations on the Primary Pustular Lesion

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IT IS the purpose of this paper to present observations concerning the primary pustular lesions of cutaneous diphtheria. The importance of early recognition of this disease is undisputed. Delay of a week in diagnosis, and consequently in specific treatment, may mean delay of a month in recovery. The pustular lesion has been mentioned previously in the literature, but its importance has not been sufficiently stressed, if recognized it will materially aid the early diagnosis of cutaneous diphtheria.

Concerning the pustular lesion, Livingood and his co-workers¹ said, "It is reasonably certain that the lesions in some individuals had their onset *de novo* in precisely the same manner as an ordinary impetiginous pustule." Cameron and Muir² in discussing acute cutaneous diphtheria, said, "The first clinical sign in such cases was a small blister or pustule centered around a hair follicle, after rupture a flat shallow sore developed with base almost flush with skin and edge composed of skin only." They remarked that these lesions were usually associated with positive nasopharyngeal cultures for diphtheria. The lesions observed healed with little residual change in the skin.

Two cases are presented which illustrate the development of the early pustular lesions of cutaneous diphtheria. They are taken from a collection of 9 cases of cutaneous diphtheria seen at the 97th General Hospital, Frankfurt a M. Germany, from March 1946 through December 1946.

REPORT OF CASES

CASE 1—A 19 year old white soldier was admitted to the venereal disease ward on May 2, 1946. A diagnosis of primary syphilis was made on the basis of a penile lesion, which showed *Treponema pallida* on the dark field. The history revealed no previous venereal disease, the serologic reactions were negative. The physical examination did not reveal complicating factors. Treatment with 4,000,000 units of penicillin was given from May 2 through May 12 with excellent clinical response.

1 Livingood, C S, Perry, J D, and Forrester, J S. Cutaneous Diphtheria. A Report of One Hundred and Forty Cases, *J Invest Dermat* 7 341 (Dec) 1946

2 Cameron, J D S, and Muir, E G. Cutaneous Diphtheria in Northern Palestine, *Lancet* 2 720 (Dec 19) 1942

On May 4 a small pustule on the right leg, laterally and just below the knee, was observed. A simple protective dry dressing was applied. The lesion gradually enlarged over a two week period to a lipomatous tumor. It was approximately 7 cm across, the elevation was about 2 cm. On May 22, the lesion was removed, revealing a clean granulating base. Microscopic examinations showed many bacteria resembling *Corynebacterium diphtheriae*. Subsequent cultures and smears of the lesion, performed after local treatment had been instituted, were negative. Nose and throat cultures were also negative for *C. diphtheriae*.

By June 6 the lesion on the leg was healing nicely. However, the patient then had a staggering gait, loss of ocular accommodation, paresthesias of the hands and feet, a positive reaction to the Romberg test and slurring of speech. On June 13 the reaction of the blood to the Kahn test was negative, the spinal fluid examination showed 200 mg of protein per hundred cubic centimeters and 3 lymphocytes per

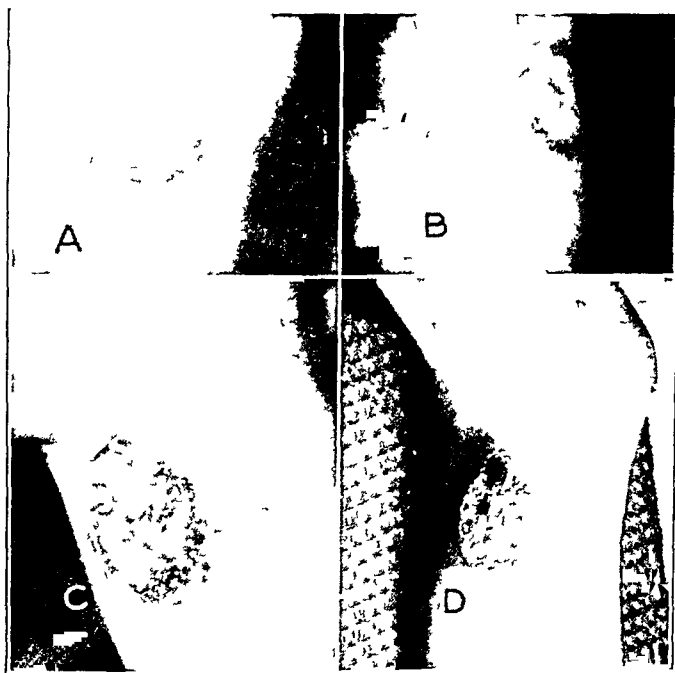


Fig 1 (case 1) —A, appearance of the lesion on May 14, 1946, ten days after its first appearance. It was of the acute type, later ulcerative. (The nose and throat cultures were negative.) B, photograph of the ulcer from another view. C, appearance of the base of the lesion on May 18. D, appearance of the ulcer on June 6, four weeks after onset, in a stage of healing. (Photography by T/4 Robert Gelberg, United States Army Photographic Service.)

cubic millimeter, but no other abnormalities. The sedimentation rate was 11 mm per hour. The temperature, pulse rate and respiratory rate had remained normal.

A careful review of the history revealed no recent episodes of sore throat or tonsillitis. The patient had been completely well prior to his admission. In his outfit, however, several men had had tonsillitis within a week of this patient's admission. The disease in 1 of these was subsequently diagnosed as diphtheria.

Since it first was thought that the complications might be due to syphilis, penicillin therapy was restarted, in addition to therapy with thiamine 50 mg daily and supportive measures. Fifty thousand units of penicillin were given every three hours for a total of 2,000,000 units only, since no improvement followed this dosage.

By June 25 there were increasing weakness of the legs and decided weakness of the right deltoid, but ocular accommodation had improved. By June 30 the weakness of the right arm had progressed to involve the deltoids and triceps bilaterally.

Since no rapid improvement could be expected, the patient was transferred to the Zone of the Interior. The final diagnosis was (1) syphilis, primary, new, (2) cutaneous diphtheria, and (3) neuritis, postdiphtheritic, peripheral and central, secondary to the cutaneous diphtheria. The differential diagnosis included the Guillain-Barre syndrome. This clinical entity could be ruled out on clinical



Fig 2 (case 2)—Acute ulcerative lesion. There are multiple small ulcers at sites of original vesicle formation. (The nose and throat cultures were negative.)

grounds. The development and progression of the neuritis in this case were typical of cutaneous diphtheria.

CASE 2—A 20 year old white soldier was admitted to the contagious disease section on Nov 10, 1946. A diagnosis of cutaneous diphtheria was based on the presence of five small ulcers located on the left leg, anteromedial surface, below the knee. These were rounded and punched out, extended through the dermis and were surrounded with approximately 0.5 cm of erythema. Cultures were taken from the base of the ulcers and were later reported positive for *C. diphtheriae*, gravis type. Results of virulence studies on guinea pigs were reported positive by the United States Army 4th Medical Laboratory.

Diphtheria antitoxin, 100,000 units, was given immediately, and warm wet dressings were applied continuously. For the first two days the disease process continued. In the immediate surrounding area, groups of small superficial pustules appeared. When the lesions were opened for culturing, a thin white fluid material was revealed. For two days new pustules appeared, despite the presence of continuous wet dressings over the area. These pustules ulcerated to give the clinical appearance seen in figure 2. This patient improved rapidly after the first week. The lesions responded to treatment with continuous warm wet dressings. Later, sulfadiazine paste containing penicillin was used. No complications developed.

COMMENT

From the evidence presented in the 2 cases, it is felt that the pustule may be the initial lesion of primary cutaneous diphtheria. If this is true, then an aid to the early recognition of cutaneous diphtheria has been established. It may be mentioned here that 2 other patients in this group recalled that a pustule had been present early in the course of the disease.

The term secondary cutaneous diphtheria is correctly applied to wound diphtheria. It is also applicable to cutaneous diphtheria when an abrasion or cutaneous lesion was present before invasion of *C. diphtheriae*. The term primary cutaneous diphtheria should be reserved for the *de novo* diphtheritic infection.

Depending on the cutaneous reaction of the host there would seem to be no reason why the initial pustular lesion should not develop into either the ulcerative or the eczematoid type. The patients reported happened to exhibit ulcerative lesions. While the condition in the second case is illustrative of the more typical lesion, the condition in the first case may reveal the final stage of a diphtheritic pustular lesion when not irritated or treated locally in any manner.

Early recognition of any form of diphtheria is imperative. This is true because the diphtheria antitoxin to be of value must be given within a week of the onset. The value of this therapy decreases with delay. From more than 200 cases of diphtheria³ observed during the interval mentioned, serious postdiphtheritic complications developed in only 4. All 4 patients had cutaneous diphtheria without clinical evidence of nasopharyngeal diphtheria. None of these received diphtheria antitoxin sooner than four weeks from the onset of the disease. For this reason recognition of the initial pustular lesion of cutaneous diphtheria has been emphasized. A suspicion of diphtheria at the onset of such a lesion may save months of hospitalization for the patient.

SUMMARY

Two cases of cutaneous diphtheria are reported with the initial pustular lesion of the primary type infection. Early recognition of this initial lesion is discussed as an aid to diagnosis of cutaneous diphtheria.

TRANSVERSE NET IN THE DIAGNOSIS OF ONYCHOMYCOSIS

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RELATIVE to the diagnosis of onychomycosis, various features have been described concerning such characteristics as the color and the shape of the nail. However, there exists no clinical feature sufficient in itself to enable one to determine mycotic causation. Microscopic examination with the observation of spores and mycelial threads and growth on culture mediums alone furnish convincing proof for this diagnosis.

In 1939, at the meeting of Polish Dermatologists held in Vilna Poland, I read a paper on a feature, hitherto unpublished, which makes definite clinical diagnosis possible. This phenomenon does not exist in all cases but when present is pathognomonic. This phenomenon consists of a delicate white net arranged parallel to the transverse axis of the nail. It is visible through a magnifying glass, but only after a drop of cedar oil has been applied. This sign is shown in figure 1. A fragment of this nail, examined under the microscope with partially closed diaphragm, is seen in figure 2. This photomicrograph shows the threads of the net arranged at various levels of the nail plate.

The question of the origin of this net arises. The white threads do not, as might be supposed, correspond to mycelial elements. Examination and measurement in several cases have shown the threads of the net to have a breadth of 10 to 20 microns, while the thickness of mycelial filaments does not exceed 2 to 4 microns.

My histologic examinations of diseased nail plates have convinced me that mycelia grow among the nail cells. Afterward, because of consumption of nail substance, an air space is formed. Thus, after a time, one sees the fungus lying on the bottom of a tunnel 10 to 20 microns wide. It is also rather characteristic that the fungus shows signs of degeneration at this time. It is obvious that what is seen clinically is a network of air spaces within the nail plate.

In view of the transverse direction of the net, one sees only cross sections of the tunnels in longitudinal sections of the nail. Cross sections of nail allow one to visualize the growth of the fungus and development of the air spaces. Figure 3 demonstrates the histologic

From the University of Posen, Poland

picture of a nail plate showing this transverse net phenomenon. This picture shows the basal layer of the plate which borders on the nail bed (not shown here). Long beads of the fungus can be seen in



Fig 1—Transverse white lines due to *Trichophyton asteroides*



Fig 2—The transverse net transilluminated. The arrow indicates the direction of the nail growth.

the chinks between nail tissues. In addition is seen a tunnel 24 microns in width, and on its bottom can be seen fungi showing distinctive features of degeneration.

Having found this sign in several nails after removal, I was encouraged to make further microscopic investigations. I found in that part of the nail proximal to the net, i. e., in the seemingly unaltered nail, a great many mycelial threads visible only under the microscope (magnification 60) and with the diaphragm partly shut. These are the places where fresh growth of fungi occurs, but the air tunnels are not yet produced.

The transverse net is best seen when its constituent threads are not set too close together. When these threads are piled up in layers, an opaque white spot can be seen clinically. Such pictures were described by Ravaut and Rabeau¹ in 1921 and Jessner² in 1922. However, on close examination under oil, especially on the border of the spot, the structure of the transverse net can be seen.



Fig 3—Photomicrograph of a transverse section of the nail plate in the case previously illustrated. *A*, mycelium in a chunk of the nail substance, *B*, degenerated mycelium in the bottom of a tunnel.

As previously mentioned, this sign of the transverse net does not occur in all cases of onychomycosis, but is evident in a substantial number of them. It is seen most often in trichophytosis of the nails. In favus the sign is seldom encountered. In a case of favus, among eight involved nails, the transverse net was seen in only one.

The net visible in the oil drop grows out simultaneously with the nail and ultimately is shed. This last point would favor a self-limited

1 Ravaut, P., and Rabeau, H. Sur une forme speciale de trichophyte ungueale, *Ann de dermat et syph* **2** 363, 1921.

2 Jessner, M. Ueber eine neue Form von Nagelmykosen (Leukonychia trichophytica), *Arch f Dermat u Syph* **141** 1, 1922.

disease in onychomycosis. This is obviously not the case, and further investigation reveals the reason. Under the microscope the fungi can be seen to grow in two directions. The transverse type of growth has been described previously. In addition to this, there can be seen in the lower layers of the nail, especially in its longitudinal ridges, fungous growth extending proximally. Figure 4 shows a portion of

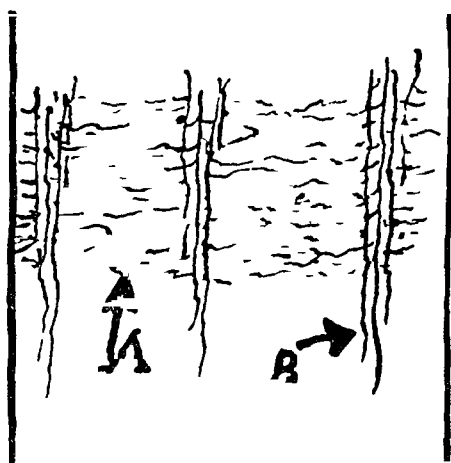


Fig 4—A fragment of the nail. A, superficial lines are visible (transverse direction). B, deeper lines are invisible (proximal direction). The arrow indicates the direction of the nail growth.

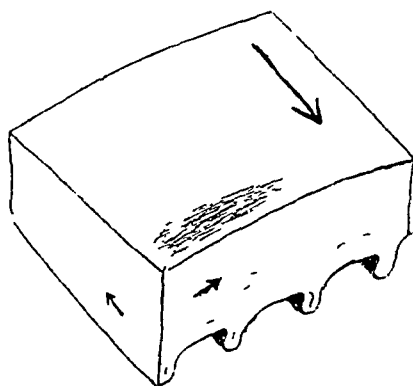


Fig 5—Schematic drawing of a segment of the nail plate. The large arrow indicates the direction of the nail growth and the small arrows the direction of the growth of the fungus.

an extracted nail under the microscope and with reduced light. Here are seen numerous transverse threads situated in the upper strata. At right angles to them are seen the longitudinal threads, few in number, the growth of which corresponds to the nail ridges. The former, transverse threads, are visible under clinical observation. The latter are imperceptible in this manner. The schematic drawing, figure 5, shows in what way the fungus grows.

The prognosis of the disease depends on the rapidity with which the fungus invades the longitudinal ridges. If the growth of the fungus remains in equilibrium with the growth of the nail, the disease may persist for years.

My histologic investigations will be published later in more detail. They prove that the fungi grow most of all in the intercellular substance of the nail. The direction of growth depends on the cellular structure in the various parts of the nail plate.

Concerning terminology, I propose the morphologic title "*leukopathia unguis mycotica*." The term *leukonychia* should be reserved for the common "gift spots." The etiologic name should be *onychomycosis leukopathica*.

SUMMARY

A pathognomonic sign of onychomycosis, the transverse white net is described. This phenomenon is visible in the majority of cases of fungous infection of the nail, but only with magnification and through an oil drop. The white lines correspond to air-filled tunnels in the nail plate. Besides these visible transverse spaces there are deeper-laid invisible shafts, extending proximally in the nail ridges. Photomicrographs of a case of onychomycosis due to *Trichophyton asteroides* are presented and are illustrative of the point.

GRENZ RAY (SUPERSOFT ROENTGEN RAY) THERAPY OF CUTANEOUS DISEASES

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THREE groups of patients with various dermatoses treated with grenz rays (supersoft roentgen rays) are presented in order to compare results with those obtained with conventional, superficial (low voltage) roentgen radiation¹

Fifty-eight patients were treated with 76 series of irradiations. A series of irradiations is the exposures given to one patient during any given period. Thirteen patients received more than one series of treatments when first one area and later a second or more areas were irradiated. In these 76 series of treatments, 29 resulted in clearing, 30, in considerable improvement, with almost complete cure, 8 in improvement, 3, in only slight improvement, and 6, in no change (table 1).

The grenz irradiation was produced in a self-rectifying vacuum tube with a thin window of pyrex glass. The electric potentials used were 12 and 14 kilovolts. In grenz ray therapy, however, the thickness of the window acting as a filter determines the quality of the rays.

The grenz ray machine used in this study is manufactured by the X-Ray Manufacturing Corporation of America, New York.

From the Department of Dermatology, New York University College of Medicine, and the Dermatological Service of the Third (New York University) Medical Division, Bellevue Hospital, service of Dr. Frank C. Combes.

1 (a) MacKee, G., and Cipollaro, A. Present Status of Cutaneous X-Ray, Grenz-Ray, and Radium Therapy, *Bull. New York Acad. Med.* **11** 383 (June) 1935. (b) Eller, J. J., and Bucky, G. The Use of the Grenz-Rays in Dermatologic Conditions, *Arch. Dermat. & Syph.* **17** 221 (Feb.) 1928. (c) Wise, F., and Sulzberger, M. Grenz-Rays, in the 1935 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1936. (d) White, C. Grenz Rays in Dermatology, *Arch. Phys. Therapy* **18** 139 (March) 1937. (e) Bluefarb, S. Therapeutic Value of Grenz-Ray in Dermatology, *ibid.* **25** 400 (July) 1944. (f) Ryan, C. Grenz-Ray Therapy in Dermatology, *Brit. J. Dermat. & Syph.* **54** 47 (Feb.) 1942. (g) Kalz, F. Theoretic Considerations and Clinical Use of Grenz-Rays in Dermatology, *Arch. Dermat. & Syph.* **43** 447 (March) 1941. (h) Wood, F. C., and MacKee, G. Therapy with Long Wavelength X-Rays (Grenz Rays), *J. A. M. A.* **96** 111 (Jan. 10) 1931. (i) MacKee, G. Telangiectasia Caused by Grenz Rays, *Arch. Dermat. & Syph.* **24** 926 (Nov.) 1931. (j) Bucky, G. Grenz Ray Therapy, New York, The Macmillan Company, 1929.

produced to a greater degree than does the kilovoltage. Accordingly, only the use of half-value layers² gives a satisfactory means for comparing the radiation qualities, which in my series of treatments were

TABLE 1—*Diagnosis and Results of Grenz Ray Therapy in 76 Series of Treatments of Cutaneous Diseases*

Diagnosis	Total Number	Grenz Ray	
		Results *	Number
Acne conglobata	1	—	1
Acne vulgaris	3	+++	3
Dermatitis, contact			
Acute	5	++	1
		++++	4
Subacute	8	+++	6
		++++	2
Chronic	9	++	2
		+++	4
		++++	3
Dermatitis hypostatica	6	++	2
		+++	1
		++++	3
Dermatosis, exudative discoid and lichenoid chronic (Sulzberger and Garbe)	1	++	1
Erythema induratum (Bazin)	1	++	1
Folliculitis, chronic pustular	1	—	1
Granuloma inguinale	1	—	1
Intertrigo	3	+++	2
		++++	1
Lichen planus			
Hypertrophic	1	+++	1
Simple	2	+	1
		+++	1
Neurodermatitis circumscripta	4	+++	3
		++++	1
Neurodermatitis disseminata	3	+++	2
		++++	1
Pain, postherpetic	1	+	1
Pompholyx, with secondary infection	2	+++	2
Pruritus ani	3	+++	1
		++++	1
		—	1
Pruritus ani et vulvae	2	+++	1
		++++	1
Psoriasis	14	+++	1
		++++	13
Sarcoma, ulcerated, Kaposi's	1	—	1
Scar, pruritic	1	—	1
Sycosis vulgaris	1	—	1
Xeroderma, with pruritus	2	++	1
		+++	1
	—	—	6
		+	3
		++	8
Total	76	+++	30
		++++	29

* Symbols of results of treatment used in this table, and in the accompanying tables, are as follows: — indicates no change, +, slight improvement, ++, improvement, +++, considerable improvement (almost cleared, but patient was either still under treatment or failed to return for final observation and discharge), ++++ cleared (patient discharged).

0.024 and 0.028 mm (24 and 28 microns) of aluminum. The half-value layer is that thickness of matter (aluminum in this report) that absorbs 50 per cent of the radiation beam. Except where otherwise noted,

2 (a) Kalz¹³ (b) Bucky¹⁴ (c) Ebbehøj, E. Untersuchungen über ultra-weiße Röntgenstrahlen, ihre Tiefendosiskurven und das Verhältnis zwischen ihren biologischen Wirkungen, Copenhagen, Nyt Nordisk Forlag, 1937.

patients received 100 r doses of roentgen rays at 95 kilovolts weekly and 270 r doses of grenz rays twice weekly

According to the absorption curves published by Ebbehøj,^{2c} approximately 94 per cent of the grenz rays at a half-value layer of 26 microns of aluminum is absorbed in the uppermost 3 mm of normal skin and practically 100 per cent within the first 5 mm. It is this lack of penetration to the deeper structures which accounts for the safety of grenz rays. This property is recognized by authorities³ on dermatologic roentgen therapy, who state that grenz radiation is a useful adjunct to roentgen rays in treatment of the eyelids, scalp and scrotum. Early objections to the restricted field of treatment are no longer valid, since the field diameter of the present grenz ray tube is three fourths of the target-skin distance.

Local therapy had been given most patients, with little success, prior to irradiation, and in many instances this local treatment was continued. Only half of the involved area was irradiated in most cases, so bilateral use of local therapy by the patient did not alter the comparative results. This local treatment consisted in the use of a bland emollient or a weak keratolytic ointment, patients with acne received a liquid detergent.

In table 2 are shown the results of grenz ray therapy alone in 27 patients and 29 series of treatments (group A). Nine series resulted in clearing, 8, in considerable improvement, 4, in improvement, 3, in only slight improvement, and 5, in no change.

In group B (table 3) 10 patients received 12 series of treatments, in which roentgen rays were given to the eruption on one side of the body and grenz rays to that on the other side. Two of these patients (cases 29 and 33) had recurrences several months later and were again treated with both forms of radiation. In only 1 series (case 7) were the results of roentgen irradiation better than those of grenz ray therapy, in 6 series the results were similar, while in 5 series grenz rays produced the better results. The duration of treatment with grenz rays was shorter in 2 series (cases 6 and 14), the same in 5 series and longer in 4 series. The duration of treatment in 2 of the last series (cases 29b and 32) was considerably longer because roentgen radiation had been given previously, and a full course of treatment could not be safely administered. Therapy had to be interrupted before healing was accomplished. In both patients, results with the longer course of grenz radiations were much more satisfactory.

Analysis of these 12 series of grenz ray treatments showed that 3 resulted in clearing and 9 in considerable improvement. Roentgen

3 MacKee, G., and Cipollaro, A. *X-Rays and Radium in Treatment of Diseases of the Skin*, ed 4, Philadelphia, Lea & Febiger, 1946.

TABLE 2—Results of Grenz Ray Therapy Alone

Case and Treatment Number	Diagnosis and Location	Duration	Previous Therapy and Response	Grenz Ray Therapy				Comment
				Area	Time	No of Doses	Results	
1b	Dermatitis, contact, subacute, both legs	4 mo	—	Left leg	3 wk	1	+ + +	
2b	Dermatitis, contact, acute, both hands and feet	1 wk	Slight	Right hand and foot	1 wk	8	+ + + + +	
3	Neurodermatitis circumscripta, right foot and left forearm	4 yr	—	Right foot, left arm	8 wk	15	+ + +	Course not completed
5	Intertrigo, groin	2 mo	—	Groin, scro tum	2 wk	1	+ +	Local exacerbation
9	Dermatitis, contact, acute, face, neck and left ear	10 mo	Slight	Face, neck, left ear	4 wk	11	+ + + + +	
10	Pruritus ani	1 yr	—	Anus, scro tum	4 wk	10	—	Course not completed 350 r
11	Acne vulgaris, face	1 yr	—	Face	20 wk	14	+ + +	
17	Pain, postherpetic	1 mo	—	Left side of chest	3 wk	7	+	
20	Neurodermatitis circumscripta, neck and lower part of back	3 yr	—	Neck, lower part of back	8 wk	10	+ + +	Later new areas of eruption developed
22	Scar, pruritic, face	3 yr	—	Right cheek	2 wk	4	—	Relapse, caused by constipation
24	Pruritus ani	9 mo	0	Anus	9 wk	9	+ + + + +	
27	Lichen planus(?), tongue	7 mo	—	Tongue	6 wk	6	+	
30	Dermatitis, contact, subacute, face	1 mo	Blopsy specimen (?) Slight	Face	2 wk	5	+ + + + +	350 r
36	Sarcoma, ulcerated, Kaposi's	6 yr	Maximum roentgen ray dose given	Ulcers, right foot	7 wk	14	+	
37	Pruritus ani	2 yr	—	Anus	3 wk	7	+ + +	
39	Dermatitis, contact, acute, hands	5 mo	Sensitive to roentgen rays, patch tests negative	Both hands	4 wk	9	+ +	
40	Dermatitis hypostatica, right leg	10 yr	—	Right leg	3 wk	6	+ +	Course not completed 450 r
41	Folliculitis, chronic pustular, both forearms	1 yr	Recurrence	Forearms	2 wk	4	—	
46	Granuloma inguinale	6 yr	Recurrence	Penis	7 wk	12	—	
47	Dermatitis hypostatica	7 yr	Roentgen rays —	Left ankle	8 wk	16	+ + +	Treatment irregular
48	Sycosis vulgaris	2 yr	Cleared with 1900 r of roentgen rays	Scalp, face	10 wk	12	—	
49	Dermatitis hypostatica	3 wk	erupted	Lower part of legs	10 days	3	+ + + + +	150 r
50	Psoriasis, body and scalp	10 yr	aggravated	Body, scalp	5 wk	9	+ + + + +	Course not completed
51	Dermatitis, contact, chronic, hands	2 yr	Recurrence	Both hands	5 wk	11	+ +	
54	Acne vulgaris	3 yr	Roentgen rays —	Face, forehead	20 wk	18	+ + +	
55	Neurodermatitis disseminata, flexures and groin	6 yr	0 Recurrence	Cubital and popliteal fossae, chin	14 wk	9	+ + + + +	180 r weekly
56	Pruritus ani et vulvae	8 yr	—	Vulva, anus	10 wk	12	+ + + + +	180 r
57a	Pruritus ani et vulvae	8 yr	—	Vulva, anus	14 wk	13	+ + +	180 r
57b	Psoriasis, pubis and elbows	8 yr	—	Pubis	14 wk	13	+ + + + +	180 r

TABLE 3—Results of Roentgen and Grenz Ray Therapy

Case and treatment No	Diagnosis and Location	Response to Previous Treatment	Roentgen Rays			Grenz Rays			Comment	
			Area	Time	Dose	Result	Area	Time		No of Cases
1a	Dermatitis, contact, sub acute, legs and arms	8 mo	Right arm	4 wk	5	+++	Left arm	4 wk	8	Exacerbation, right arm
6	Dermatitis, contact, sub acute, both hands	9 mo	Right hand	4 wk	5	+	Left hand	4 wk	7	Exacerbation, both hands
7	Dermatitis, contact, sub acute, hands and feet	1 mo	Right hand, foot	3 wk	4	++++	Left hand, foot	4 wk	8	Hospitalization resulted in slight improvement
14	Lichen planus, simple, both legs	2 mo	Right leg	6 wk	6	++	Left leg	4 wk	7	350 r 4 times 270 r 3 times
16	Pompholyx, secondary infection hands	6 mo	Right hand	5 wk	5	+++	Left hand	6 wk	7	Exacerbation, right leg
18	Acne vulgaris, face	8 yr	Right side of face	13 wk	15	++	Left face	13 wk	21	Left side of face responded sooner
21	Neurodermatitis circumscripta, both legs	4 yr	Right popliteal fossa	4 wk	4	+++	Left thigh	6 wk	6	450 r
29a	Intertrigo, breasts	7 mo	Right side	2 wk	3	++	Left side	2 wk	3	Exacerbation, both sides
29b	Intertrigo, breasts	1 mo	Right side	4 wk	5	++	Left side	12 wk	9	
32	Pompholyx, secondary infection, hands	6 mo	Right hand	2 wk	3	+	Left hand	8 wk	6	
33a	Dermatitis, contact, chronic, arms and legs	6 mo	Right arm, leg	8 wk	9	++++	Left arm	8 wk	12	Left arm responded sooner
33b	Dermatitis, contact, acute, arms and legs	1 mo	Right leg	3 wk	3	++++	Left arm, knee	4 wk	4	Exacerbation, 6 mo later

TABLE 4—Results of Unilateral Grenz Ray

Case and Treatment Number	Diagnosis and Location	Duration	Response to Previous Treatment	Therapy			Result	Comment
				Area	Time	No of Doses		
2a	Dermatitis, contact, acute, both hands and right foot	4 wk	Slight	Left hand	4 wk	8	++++	Right hand, right foot +
4	Lichen planus, hypertrophic, both legs	4 yr	—	Left leg	6 wk	8	+++	Right leg +
8	Psoriasis, scattered	1 yr	—	Left arm, right leg	6 wk	13	+++	—
12	Neurodermatitis disseminata, with secondary infection, both arms and hands	2 yr	Intermittent	Left arm and hand	4 wk	4	+++	Right arm, right hand +
13	Dermatitis hypostatica, both legs	15 yr	—	Left leg	5 wk	10	++	Left leg —, right leg, exacerbation
15	Dermatitis, contact, chronic, both hands	9 mo	Slight	Left hand	6 wk	8	++	Right hand +
19a	Xeroderma, right foot and leg	3 mo	—	Right leg	6 wk	11	++	Right foot —
19b	Xeroderma, right foot and leg	4½ mo	—	Right foot	4 wk	8	+++	—
23	Dermatitis, contact, acute, both hands	6 mo	Intermittent, roentgen ray no benefit	Left hand	8 wk	14	++++	Right hand +
25	Neurodermatitis circumscripta, cubital fossae	1 yr	—	Left cubital fossa	4 wk	5	++++	Right side +++++, slower
26	Erythema induratum (Bazin), both legs	15 mo	—	Left leg	3 wk	4	++	Treatment, inadequate response, right leg, —
28	Dermatitis, contact, chronic, both hands	10 yr	Intermittent	Left hand	6 wk	8	+++	Right hand, —
31	Dermatosis, exudative discoid and lichenoid chronic (Sulzberger and Garbe), generalized	4 yr	Intermittent	Left side of chest, left arm	6 wk	12	++	Right side —, left side, exacerbation several months later
34a	Dermatitis hypostatica, bilateral	18 mo	—	Left leg	8 wk	13	++++	Right leg, —
34b	Dermatitis hypostatica, bilateral	19 mo	—	Right leg	4 wk	4	++++	Other extremities, —
35a	Psoriasis, extremities	3 yr	—	Left arm	6 wk	10	++++	Legs, —
35b	Psoriasis, extremities	—	—	Right arm	8 wk	11	++++	—
35c	Psoriasis, extremities	—	—	Both legs	8 wk	8	++++	—
35d	Psoriasis, extremities	—	—	Right hand	8 wk	13	+++	Left hand, —
38a	Dermatitis, contact, subacute, hands	1 yr	—	Left hand	8 wk	7	+++	—
38b	Dermatitis, contact, subacute, hands	—	—	Left side of scalp	18 wk	17	++++	350 r, irregular treatment
42a	Psoriasis, scalp and body	3 yr	—	Right side of scalp	12 wk	9	++++	350 r, irregular treatment
42b	Psoriasis, scalp and body	—	—	Middle part of back, right	5 wk	4	++++	100 r, irregular treatment
42c	Psoriasis, scalp and body	—	—	anterior thorax	1 wk	2	++++	100 r
42d	Psoriasis, scalp and body	—	—	Left posterior axilla	5 wk	10	++++	180 r
42e	Psoriasis, scalp and body	—	—	Lumbar portion of spine	1 wk	2	++++	190 r
42f	Psoriasis, scalp and body	—	—	Left midaxilla	8 wk	12	—	—
43	Acne conglobata	2 yr	—	Right side of back	3 wk	6	+++	190 r, in hospital 1 mo previous to treatment
44	Dermatitis, contact, subacute, face and hands	1 yr	—	Right side of face, right hand	3 wk	7	++++	Local exacerbation
45a	Dermatitis, contact, chronic, lichenified, both thighs	8 mo	—	Left thigh	12 wk	19	+++	—
45b	Dermatitis, contact, chronic, lichenified, both thighs	2 mo	—	Right thigh	9 wk	16	++++	Right side of scalp, —
52a	Psoriasis, scalp	—	—	Left side of scalp	5 wk	9	++++	—
52b	Psoriasis, scalp	—	—	Right side of scalp	2 wk	4	+++	Right hand, —
53a	Dermatitis, contact, chronic, hands	30 yr	Intermittent	Left hand	3 wk	6	+++	—
53b	Dermatitis, contact, chronic, hands	29 yr	Intermittent	Right hand	1 wk	8	+++	190 r
58	Neurodermatitis disseminata, torso, arms and face	—	—	Left side only	—	—	—	—

irradiation resulted in clearing in 3 series, in considerable improvement in 3 series, in improvement in 4 series, and in slight improvement in 2 series

In table 4, 22 cases are listed, representing the 35 series in group C in which grenz radiation was given to only one of the involved areas, the remaining areas being used as controls. When the eruption was of equal severity on the two sides, treatment was begun on the left side, otherwise, the area of greater severity was selected.

Of the 35 series of treatments, 17 resulted in clearing, 12 in considerable improvement, 5 in improvement, and 1 in no change. Of the patients with untreated areas, only 1 (case 25) was healed with topical applications and 5 showed slight improvement. Eight series of irradiations were given to the remaining eruption after the initially irradiated areas had been cleared. These, therefore, could no longer be compared with an untreated area.

CASES OF SPECIAL INTEREST

CASE 2—The patient was first seen with lesions of pruritic, weeping, vesicular, erythematous contact dermatitis on both hands and the dorsum of the right foot, all of which had been under treatment with compresses and bland ointments for four weeks. Two exposures of grenz rays to the left hand was followed by such improvement that the emollient-fixed dressing was discontinued, but only on that hand. In two weeks, after four treatments, the subjective and objective difference between the two hands was remarkable. In four weeks the left hand was healed, while the right hand and foot were eczematized and fissured, despite the continuous use of a fixed dressing. At this time, grenz ray therapy was begun on these areas, which were symptomatically relieved in two weeks and cured in six weeks.

CASE 31—A patient with exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe) of four years' duration was given twelve exposures to the left arm and the left side of the thorax. Despite obvious objective improvement, with drying and healing of the patches on the left side only, the patient complained of continued pruritus. He showed no evidence of excoriation, however, and therapy was discontinued.

CASE 35—A patient with psoriasis en plaque involving all extremities had made no response to local therapy for three years. Grenz radiation was given to the left arm. When the eruption in this area cleared, the right arm, and later the legs, were treated. Each area cleared independently after it had received about ten exposures within five to six weeks. The areas treated showed moderate hyperpigmentation, which disappeared after about two months. Ten months later, a check showed that no relapses had occurred.

CASE 42—A patient with guttate psoriasis of the trunk and scalp and two large plaques over the lumbar portion of the spine was treated with grenz rays in six series. The scalp was irradiated for eighteen weeks. The itching was rapidly relieved, and the lesions finally cleared completely. The guttate lesions of the thorax were treated in four groups, and each cleared independently after two to four treatments. No lesions had recurred when the patient was discharged, five months later.

CASE 55—A girl aged 6, with neurodermatitis disseminata involving the flexures, groins and face, received one field of exposure on the cubital areas, which cleared after three to four treatments. Here the eruption persisted just above and below the 6 inch (15 cm) field. Treatment of the skin above and below the elbow in two fields resulted in healing of the entire area. The eruption on other areas not then treated persisted until treated later.

CASE 58—A patient with neurodermatitis disseminata involving the entire body above the waist was given grenz rays on the left side only. On the abdomen and chest, the eruption and pruritus cleared within the circle of the exposed field only. There was considerable hyperpigmentation of the skin prior to irradiation, the pigmentation was increased in the areas after grenz ray therapy.

SUMMARY

Seventy-six series of treatments with grenz rays of 58 patients produced the following results: Twenty-nine resulted in clearing, 30, in considerable improvement, 8, in improvement, 3, in slight improvement, and 6, in no change.

Patients with twenty diseases of the skin represented in this report were sent in for treatment from the general dermatologic clinic after their failure to respond satisfactorily to local therapy.

Three methods of therapy were presented, (a) use of grenz rays (supersoft roentgen rays) only, (b) treatment of one half of the eruption with roentgen and of the other half with grenz rays, (c) grenz ray treatment of only one half the area involved.

Several case histories of special interest are reported.

CONCLUSIONS

- 1 The 76 series of treatments with grenz rays (supersoft roentgen rays) show results which compare favorably with published reports of diseases of the skin treated with roentgen rays.

- 2 In the group in which both modalities of radiation were given the same patient, the results were slightly in favor of the grenz rays.

- 3 Treatment of grenz rays with a half-value layer of 0.028 mm (28 microns) or less of aluminum appears to be a safe form of physical therapy.

- 4 Grenz ray therapy is especially useful for superficial diseases of the skin. Controlled treatment eliminates the possibility of a psychotherapeutic effect in those diseases in which such an effect might occur.

11 East Sixty-Eighth Street

RECURRENT HERPETIFORM DERMATITIS REPENS

Report of a Case

MAX POPPER, M D
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THE LITERATURE on this comparatively new entity, first described by Ayres and Anderson under this name,¹ has been summarized recently by Sachs, Hyman and Gray.² Although Pels and Goodman³ were probably the first to describe this condition, they regarded it only as a variant of Darier's disease (keratosis follicularis). Priority has been accorded to Hailey and Hailey,⁴ who were the first to consider this disease as a dermatologic entity. There is, however, no agreement on the classification of the disease, and thus a considerable number of names have been suggested. While observers agree on the identity of the clinical course and picture of this disease, the interpretation of the peculiar histologic features is still under discussion. This situation seems to warrant the publication of a case which I had the opportunity to observe.

REPORT OF CASE

M G, a married white woman aged 31, was first seen on Nov 28, 1945 at the Cedars of Lebanon Hospital, Los Angeles. The patient complained of a recurrent eruption of eight years' duration on the upper part of her back and her shoulders. No information as to the presence of similar lesions in other members of her family was available. The patient complained of no symptoms other than the eruption, which was decidedly pruritic. The personal history was essentially noncontributory.

Physical Examination—The patient was a well developed, healthy-appearing white woman. General examination revealed no pathologic changes other than the lesions in the skin.

Skin On the outer side of the upper part of the left arm there was an irregularly ovoid lesion about 2 inches (5 cm) in diameter. The lower part of this lesion consisted of grouped, crusted elevations and exhibited a sharply demarcated, somewhat circinate, elevated border, which in its upper portion was composed of unbroken vesicles. There was evident, though hardly visible, a

1 Ayres, S, Jr, and Anderson, N P. Recurrent Herpetiform Dermatitis Repens, Arch Dermat & Syph **40** 402 (Sept) 1939

2 Sachs W, Hyman, A B, and Gray, M B. Epidermolysis Bullosa. A Recent Described Variant, Arch Dermat & Syph **55** 91 (Jan) 1947

3 Pels, I R, and Goodman, M H. Criteria for the Histologic Diagnosis of Keratosis Follicularis (Darier), Arch Dermat & Syph **39** 438 (March) 1939

4 Hailey, H, and Hailey, H. Familial Benign Chronic Pemphigus, Arch Dermat & Syph **39** 679 (April) 1939

circinate, hourglass-like configuration of the upper part of the border, which extended in an upward direction, it was occasionally accentuated by remnants of crusted papules. The center of the lesion was depressed and pinkish (fig 1). The eruption on the patient's back showed a peculiar combination of pigmentation and depigmentation and two lesions clinically similar to those on the upper portion of the arm. In the right axilla there was an ill defined crusted patch extending toward the chest in a broad band, this represented remnants of a larger lesion, which had left pigmentation on involution.

Course—A biopsy specimen was taken from the lesion on the back on December 26. One roentgen ray treatment (75 r, unfiltered) was given to all the lesions on Jan 2, 1946. There was steady improvement, and on February 20 the areas were completely cleared.

Laboratory Studies—A blood count showed 4,000,000 erythrocytes, 73 per cent (12.3 Gm) hemoglobin, a color index of 0.91, 76 polymorphonuclear leukocytes, 15 lymphocytes, 2 eosinophils and 7 monocytes.

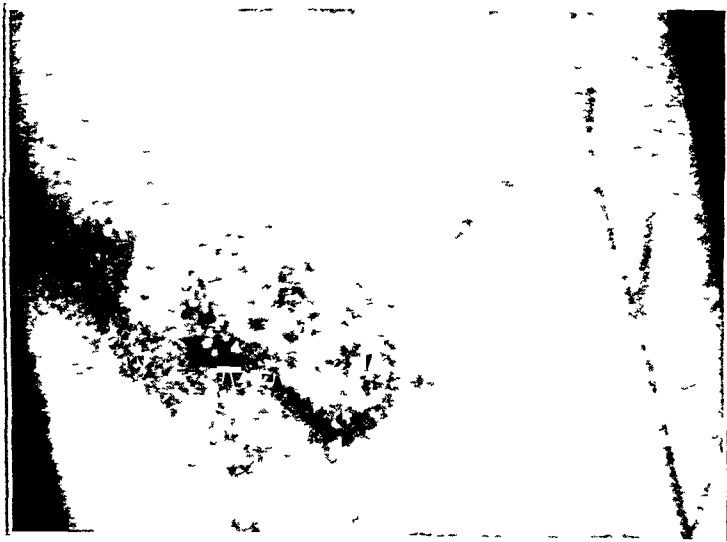


Fig 1—Lesion on the upper portion of the left arm, showing the elevated, circinate lower border, composed of unbroken vesicles and crusts.

The reactions to the Kline and Wassermann tests were negative. The specific gravity of the urine was 1.026 and the reactions for sugar and albumin were negative.

Biopsy—Slides were sent to the Army Institute of Pathology, Washington, D C, on Feb 9, 1946, by the Department of Pathology of the Cedars of Lebanon Hospital.

Report of Army Institute of Pathology *Gross Appearance* The biopsy specimen, which consisted of an elliptic segment of skin, measuring 16 by 5 mm, had been fixed in Bouin's fluid (Path Accession No 161561). Nothing characteristic was observed grossly.

Sections were prepared from two areas.

Microscopic Appearance An examination of numerous serial sections revealed stratified squamous epithelium, which was only slightly thicker than normal. There was slight parakeratosis and keratosis. The granular cell layer was slightly thicker than normal. Occasionally intraepithelial vesicles filled with inspissated, amorphous material and numerous leukocytes, chiefly polymorphonuclear, were seen.

There were numerous irregular defects in the malpighian layer. These defects were partly filled with amorphous and granular, pink-stained material, containing a few polymorphonuclear leukocytes, as well as round cells. A few desquamated epithelial cells could be seen. These were fairly well preserved in a few areas. However, there were many minute acidophilic granules in the intracellular layers, some of these lay within the cells and may have represented inclusion bodies. The papillae were relatively blunt. In the papilla or superficial portion of the corium the capillaries were numerous and moderately dilated and showed moderate perivascular infiltration with round cells. Some of these round cells were

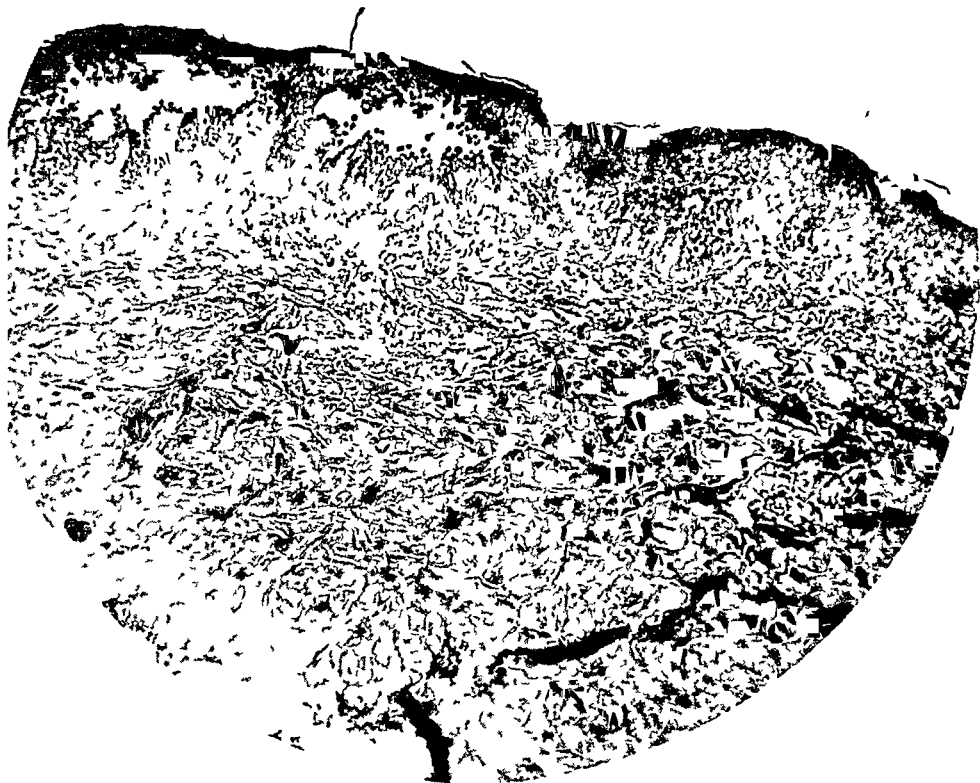


Fig 2—Low power photomicrograph, showing hyperkeratosis, a thickened granular layer and formation in the prickle cell layer of clefts containing round epithelial cells. To the right are finger-like projections of rete pegs, containing loose, disorganized, rounded prickle cells.

identified as lymphocytes, others were large and resembled macrophages. Some of the latter were elongated, and the endothelial cells of the blood vessels were plump.

Diagnosis. The disease was diagnosed as *keratosis follicularis*.

Personal Report. Before I received the report of the Army Institute of Pathology, I recorded my own histologic observations as follows:

The predominant pathologic changes were those present in the epidermis. The prickle cell layer exhibited numerous clefts with fiordlike, irregular borders. These clefts were situated in the lower part of the epidermis. The roof, therefore, was made up of a number of rows of prickle cells of apparently normal appearance, while the base was frequently represented by a single layer of basal cells. This was true of the majority of the clefts, except for some very large ones, which seemed

to occupy almost the entire thickness of the epidermis. However, the lower border of even the largest clefts was always formed by a row of basal cells. These lacunas were numerous, so much so that some were separated from one another only by small bridges of normal epidermis. Sometimes they were also seen in the broadened rete pegs. Some cells, adjacent to the clefts, seemed to be in irregular positions in relation to one another. In these cells the prickles were apparently absent, thus causing the loss of their physiologic device for regularity. Most of the clefts contained rounded, loose epidermal cells, which were scattered

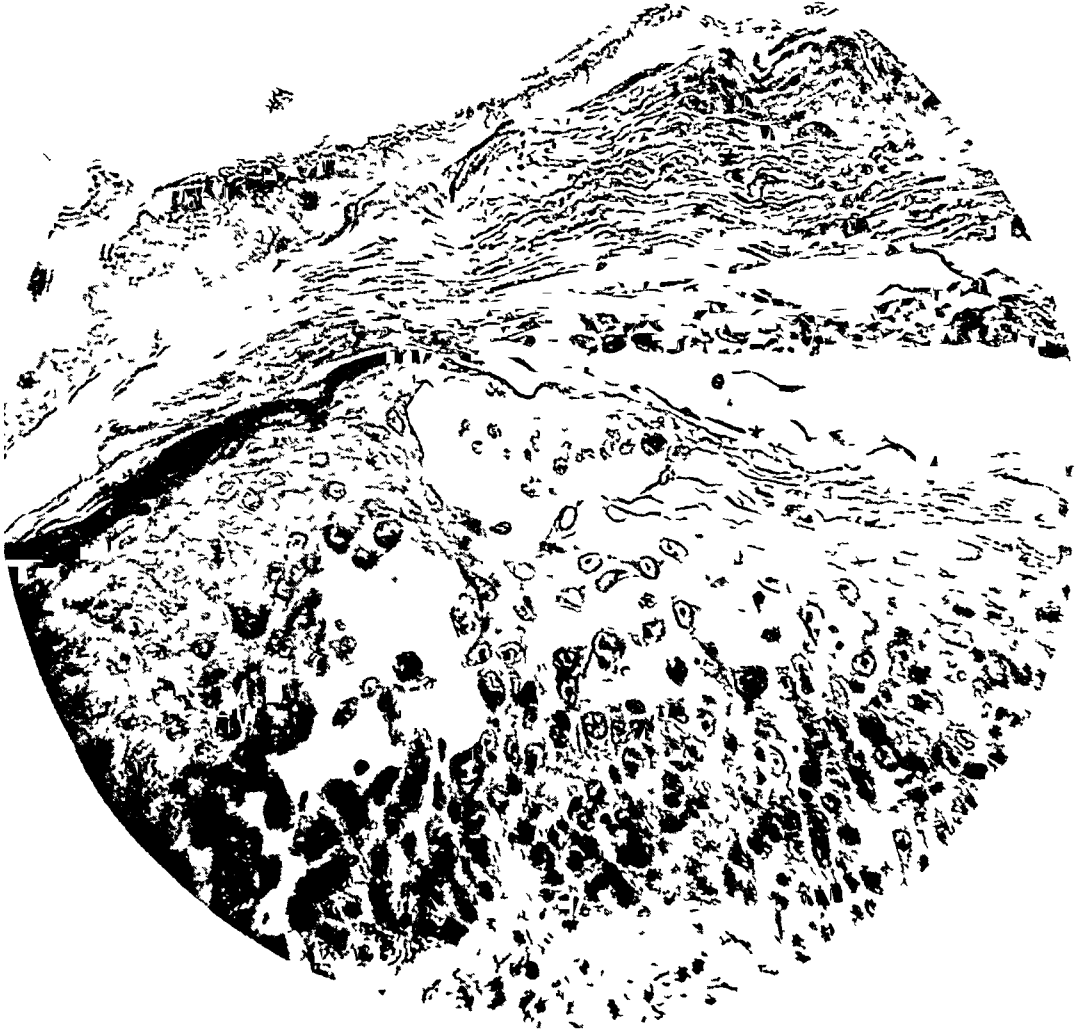


Fig 3—High power photomicrograph. Hyperkeratosis and parakeratotic scale are shown, the granular layer is absent. In the center is a subcorneal abscess containing round cells and detritus. Formation of lacunas in prickly cell layer and acantholysis are shown.

about like dice on a table. These cells could be recognized as rounded prickly cells which had lost their prickles. Occasionally eosinophilic staining of their cytoplasm was noticed. However, the nuclei were well stained and preserved, and the nucleoli were plainly visible. In addition, there were a few small abscesses in the upper part of the epidermis directly beneath the corneal layer, these were filled with leukocytes and cell detritus. The number of rows in the basal cell layer,

particularly below the clefts, was increased, mitotic figures were noticeable. Acanthosis, due partly to the proliferation of the basal cell layer, was present. The junction of the epidermis and the corium was straight in some places, whereas in others, particularly in the region of the lacunas, there were finger-like projections of the rete pegs.

The horny layer was moderately thickened and contained serum, fibrin and, occasionally, round cells and detritus. Above the site of the clefts the granular layer was either increased in size or missing. In those places where it was missing a parakeratotic scale was present, representing probably a later phase of development. The upper portion of the cutis was the site of dilated vessels and a perivascular round cell infiltrate, most pronounced beneath the site of the epidermal lacunas (figs 2 and 3).

COMMENT

The clinical picture of the disease, as described by numerous authors, has been fairly well established. The outstanding features are (1) formation of vesicles or bullae, with subsequent rupture and formation of crusted lesions, and (2) response to superficial roentgen irradiation within a short time. The clinical features seem to justify a classification of the disease as vesicular dermatitis. It is, however, due largely to the different interpretations of the histologic features that there is disagreement as to the classification of the disease.

One entity to which this disease has histologic resemblance is Darier's disease (keratosis follicularis). Ehrmann⁵ described Darier's disease as follows:

A rare disease, sometimes traceable through two or three generations, [it is] characterized by a formation of dull papules, reddish in the beginning, which are sometimes located on top of the follicles. Soon they develop into flat or bluntly conical, earth-colored papules, which rub off easily, as they consist mainly of horny material. By confluence of papules, flat plateaus develop, which are rough, slightly verrucous and earth colored.

Brunauer⁶ stated that the completely developed, typical lesion of Darier's disease is a small papule, covered with a horny scale. Atypical, and chiefly secondary to the primary lesion, is the development of vesicles, pustules, urticarial eruptions and lesions simulating lichen urticatus. Brunauer⁶ made the following statement concerning Darier's disease:

The disease is fundamentally a progressive one, while remissions and exacerbations occur, there is a tendency toward gradual progression. The disease sometimes lasts from early youth to old age. It is hardly, if at all, influenced by any form of therapy.

5 Ehrmann, S. Die Psorospermiosis cutis, Keratosis follicularis (Darier), in *Vergleichend-diagnostischer Atlas der Hautkrankheiten und der Syphilide*, Jena, G. Fischer, 1912.

6 Brunauer, St. R. Ueber Hauterscheinungen bei Morbus Darier, in *Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1927, vol 8, pt 2.

On the basis of histologic studies, Sachs, Hyman and Gray² recently attempted to show that the disease is not pemphigus, dermatitis herpetiformis or Darier's disease, but a form of epidermolysis bullosa. Incidentally, Ayres and Anderson¹ would not give the name "herpetiform

Comparative Histologic Features of Darier's Disease, Epidermolysis Bullosa and the Presented Disease

Histologic Change or Structure Involved	Darier's Disease	Epidermolysis Bullosa	Presented Disease
Stratum corneum	Considerably enlarged, follicular horny plugs present	Thinner than normal, as a rule	Moderately thickened
Parakeratosis	Present	Present	Present
Stratum granulosum	Considerably thickened in spots	Normal	Thickened in spots
Prickle cell layer	Considerably thickened	Thin, two layers as a rule	Thickened
Basal cell layer	Considerably thickened, very active, sometimes resembling pseudoepitheliomatous hyperplasia	Normal	Thickened, proliferating mitotic figures
Pigment	First increased, later diminished, dendritic melanoblasts adjacent to clefts	Increased in bullae of long standing	Normal
Epidermodermal junction	Finger like projections of basal cell layer into the rete	Normal	Normal in spots, finger like projections of rete pegs in other areas
Superficial abscess (sub corneal)	Absent	Sometimes present (Siemens, H W Arch f Dermat u Syph 134 454, 1921)	Always present
Lacunae or clefts in epidermis	Present	Present	Present
Location of lacunae	Within epidermis, lower border always formed by basal cell layer	Mostly between cutis and epidermis, lower border formed by papillary layer	Within epidermis, lower border always formed by basal cell layer
Content of lacunae	Considerable amount of corps ronds, grains (dyskeratosis) and detritus	Amorphous material, fibrin, erythrocytes, leukocytes, nuclei, eosinophils, epidermal cells (Blumer, C, cited by Brunauer ⁶)	Rounded prickle cells, sometimes resembling corps ronds, pseudo dyskeratosis (Sachs ²), or dyskeratoid dermatosis of Frank and Rein ¹¹
Cutis	Perivascular infiltrate, mostly lymphocytes, occasionally leukocytes and eosinophils, elastic fibers normal	Moderate dilatation of papillary vessels and lymph capillaries, perivascular infiltrate, elastic fibers degenerated or missing (dystrophic form)	Dilatation of papillary vessels, perivascular infiltrate, elastic fibers normal

dermatitis" to this disease because of a resemblance to Duhring's disease. They stated

Because of its resemblance to dermatitis repens and to herpes simplex, we have suggested the name "recurrent herpetiform dermatitis repens"

The accompanying table is presented to show the histologic similarities and differences of Darier's disease, epidermolysis bullosa (according to Brunauer⁶ and Riecke⁷ and the disease presented (table)

⁷ Riecke, E. Epidermolysis bullosa, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol 7, pt 2

Recently a case of bullous dyskeratosis ("familial benign chronic pemphigus") was presented by Miller and Rees⁸ before the San Francisco Dermatological Society. In the discussion, Templeton⁹ pointed out that the histologic picture was classic and could be substituted for one of the illustrations in the original description of the disease. Another case of benign familial pemphigus was presented by Lynch¹⁰ before the Minnesota Dermatological Society. In both these cases the diagnosis was accepted without controversy. Many other cases of this condition, under various names, have been reported in the last eight years, recognizable by distinct clinical and histologic features. These citations indicate that, in spite of its many similarities to other diseases, this dermatosis has distinct and characteristic features which permit an undisputed diagnosis in typical cases. I am fully in accord with the following statement by Frank and Rein¹¹ which expresses an opinion shared by Montgomery,¹² Anderson¹³ and others:

We are fully aware of the many similarities that would suggest a relation to pemphigus, Darier's disease and dermatitis herpetiformis, as has been suggested by other authors. However, it is our contention that there is not enough similarity to allow for such a point of view at present. The condition presents a definite clinical and microscopic picture that justifies its consideration as a separate entity until further observations are able to place it in a definite category.

SUMMARY AND CONCLUSION

A case of bullous dermatosis described by Ayres and Anderson¹ as "recurrent herpetiform dermatitis repens," and by others under various names, is presented.

Clinical and histologic similarities and dissimilarities between this disease and other diseases, which may be considered in the differential diagnosis, are discussed.

Until further evidence has been submitted to the contrary, it appears justifiable to consider the described condition as a distinct and separate clinical and histologic entity.

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8 Miller, H. E., and Rees, B. Bullous Dyskeratosis (Familial Benign Chronic Pemphigus), *Arch. Dermat. & Syph.* **55**: 730 (May) 1947.

9 Templeton, H. J., in discussion on Miller and Rees⁸.

10 Lynch, F. W. Benign Familial Pemphigus, *Arch. Dermat. & Syph.* **56**: 134 (July) 1947.

11 Frank, S. B., and Rein, C. R. Dyskeratoid Dermatitis, *Arch. Dermat. & Syph.* **45**: 129 (Jan.) 1942.

12 Montgomery, H., in discussion on Frank and Rein,¹¹ p. 148.

13 Anderson, N. P., in discussion on Frank and Rein,¹¹ p. 148.

ALLERGIC CONTACT DERMATITIS DUE TO RUBBER

With Special Reference to Latex

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AND

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BALTIMORE

THE IMPORTANCE of rubber as a cause of dermatitis both in its manufacture and use has received due emphasis in the literature Schwartz Tulipan and Peck¹ have written extensively on the occupational disease hazards to the skin in the manufacture of both synthetic and natural rubber In a recent article² on dermatitis due to wearing apparel, Schwartz and Peck reviewed the literature and found rubber gloves, girdles, dress shields, gas masks and condoms among the commoner rubber sensitizers Other rubber goods, such as bunion protectors,³ ear phones,⁴ art gum erasers⁵ rubber tips of stethoscopes,⁶ friction tape,⁷ adhesive tape,⁸ rubber fillers in eyelash curlers⁹ and rubber cement used in the manufacture of shoes¹⁰ have been reported as proved causes of dermatitis In our own practice, we have seen 33 proved cases of dermatitis due to rubber These were due to rubber gloves,¹⁰ rubber dress shields,² rubber guards over ear pieces of glasses,³ condoms,² elastic in hose, rubber cable, rubber baby pants and miscellaneous rubber materials

1 Schwartz, L, Tulipan, L, and Peck S M Occupational Diseases of the Skin, ed 2, Philadelphia, Lea & Febiger, 1947, p 498

2 Schwartz, L, and Peck, S M Dermatitis from Wearing Apparel, J A M A **128** 1209-1217 (Aug 25) 1945

3 Niles, H D Dermatitis Due to Rubber Bunion Protector, J A M A **97** 778 (Sept 12) 1931

4 Thomas, R B, and Smith, T W Report on Sensitivity to Rubber Earpieces on Headphones, Air Surgeon's Bull (no 5) **1** 11 (May) 1944

5 Adkinson, J, and Walker, I C A Patient Sensitized to Art Gum Eraser, J A M A **101** 2117-2118 (Dec 30) 1933

6 Halloran, C R Contact Dermatitis Due to Rubber Tips of Stethoscope, Arch Dermat & Syph **36** 140-141 (July) 1937

7 Schwartz, L, and Albaugh, R P Dermatitis in Nut and Bolt Plant Due to Use of Friction Tape, Pub Health Rep **49** 1051-1056 (Sept 7) 1934

8 Schwartz, L, and Peck, S M Irritants in Adhesive Plaster, Pub Health Rep **50** 811-819 (June 14) 1935

9 Curtis, G H Contact Dermatitis Caused by an Anti-Oxidant in Rubber Fillers of Eyelash Curlers Report of Seven Cases, Arch Dermat & Syph **52** 262-265 (Oct) 1945

10 Gaul, L E Personal communication to the authors

REPORT OF TWO CASES

CASE 1—Mrs M B, white woman, aged 25, was first seen in March 1942, complaining of a severe eruption in the axillas that followed the wearing of a pair of dress shields. She gave a history of having a weeping eruption of the dorsa of her feet the previous summer, which she attributed to the rubber straps of her bathing sandals. The patient presented an extensive, severe, erythematous weeping and vesicular dermatitis in both axillas. Patch tests were made with the cloth on the dress shields as well as with the rubber lining, and both resulted in a 3 plus reaction. The patient was again seen in 1945, at which time she presented an extensive weeping vesiculobullous dermatitis involving the hands, wrists and forearms and to a lesser extent the arms, neck and face. The eruption appeared within twenty-four hours after she had worn a pair of synthetic rubber gloves and was so severe that she was incapacitated for two weeks. She had first inflated the gloves by blowing into them and wore them for only ten minutes. In July 1945 there appeared across the dorsal surface of each foot a bandlike group of vesicles after she had worn a new pair of play shoes. About a year later, after she had worn a pair of sandals, this same picture was reproduced, with the addition of acute vesiculation of the soles.

The manufacturer of the rubber gloves in question was contacted in an attempt to determine the sensitizing agent. She was tested with six samples of synthetic rubber, and, although she was found to be sensitive to three, we were unable to determine from these tests the exact offending ingredient. Since then, we learned from our patient that she was able to use rubber gloves made of neoprene® (a polymer of chloroprene, a synthetic derivative of acetylene) latex from another manufacturer without difficulty. The result of a patch test to a crude neoprene® (synthetic) latex® was negative.

CASE 2—Mrs C Z, a white woman aged 35, was observed with an acute generalized eruption, which first appeared and was worse on the flexor surface of the forearms. There was also extensive involvement of the arms, neck and face. The eruption was a diffuse edematous nonvesicular dermatitis which appeared two weeks before she was observed by us. She attributed her symptoms to a permanent wave which she had received a day prior to the onset of the eruption. This was ruled out because the scalp was entirely free. No definite history of other allergenic contactants could be elicited. A striking feature was the complete bilateral symmetry of the acute edematous and erythematous non-eczematous eruption of the flexor surfaces of the forearms, which stopped abruptly at the cubital spaces. A week of soothing therapy produced only slight improvement. After much discussion, because the location of the eruption suggested irritation from holding her baby, a patch test was made with her baby's rubber pants, which caused a 3 plus reaction. The patient then recalled that at the time of the onset of the eruption she had changed the brand of her baby's pants, because she was unable to obtain the type ordinarily used. After discarding the offending brand of rubber pants, recovery was rapid and complete.

According to the label, the incriminated rubber pants were manufactured from "creamy neoprene latex." Several attempts were made to obtain the ingredients used in the manufacture and processing of this rubber in order to trace the offending material, but the manufacturer was uncooperative. Subsequently, patch tests were performed with four other brands of pink baby pants made of synthetic latex, including the type the patient used without difficulty. Tests with the latter brand gave negative reactions while tests with the other three gave 1, 2 and 3 plus reactions, respectively.

COMMENT

According to Schwartz and his co-workers,¹ up to 1926 dermatitis due to rubber was prevalent, but since then the number of cases has materially diminished because many rubber manufacturers have discontinued the use of well known irritating accelerators and antioxidants

During World War II, the manufacture of synthetic rubber was begun on a large scale in this country. Its widespread use had undoubtedly caused many cases of dermatitis. However, scant reference has been made in the literature to specific cases of dermatitis produced by synthetic rubber.

Most of the dermatitis produced in the users of rubber goods is probably the result of handling the latex form of rubber from which are manufactured gloves, all-rubber girdles, condoms and similar articles. Synthetic latex, according to Schwartz and his co-workers,¹ is more likely to cause dermatitis, because, in addition to the accelerators, antioxidants and other compounds used in the processing of both synthetic and natural rubber, the former also contains more uncombined and unpolymerized chemicals. In natural rubber these antioxidants and accelerators were long known to be the actual cause of the dermatitis, rather than the rubber itself. In addition to these chemicals, in synthetic rubber "something new" has been added. However, we did patch tests in 5 of our cases in which there was sensitivity to rubber with crude neoprene[®] (synthetic) latex[®] obtained from the Dupont company, which gave negative results.

Among the difficulties encountered in tracing the irritating ingredient in rubber, natural or synthetic, is the fact that many rubbers are "vapor cured" with sulfur monochloride. With this method of processing, according to Schwartz and his co-workers,¹ compounds are formed continuously on the surface of the rubber, and these compounds may be the irritants or sensitizers. In addition, in some rubbers the accelerators are incorporated loosely and are leached out by perspiration or, when contained in too large a quantity, "bloom out," whereas ordinarily they could cause no trouble.

To learn the specific offending substance, Schwartz and his co-workers¹ stated, "the rubber may be traced to the factory and information can be obtained concerning the accelerators, anti-oxidants and other compounds in the rubber. Patch tests with these substances usually reveal the irritant." From our experience, it is not as simple as herein stated not only because of the poor cooperation of the manufacturers but also because of the "leaching and blooming out" processes described herein and the irritating or sensitizing compounds that may be continuously formed on the surface of certain "vapor-cured" rubbers.

The cases of dermatitis herein reported were specifically caused by synthetic rubber. In the first case, the cause was readily apparent and was produced at the slightest contact with different types and forms of rubber. Blowing into a pair of rubber gloves, for example, produced an extensive and severe dermatitis of the face. In the second case, the offending agent was not so evident. A casual and entirely unsuspected article was at fault. On thorough questioning, the patient stated that she "did nothing" which could possibly cause her dermatitis, a phrase one hears so often in trying to trace dermatitis-producing contactants. Here, an article of wearing apparel produced no dermatitis in the wearer, i e., the baby, but did cause a severe and extensive eruption in an innocent (but interested) bystander.

SUMMARY

Two cases of extensive dermatitis due to contact with synthetic rubber are reported. In 1 case the hypersensitivity due to rubber was so severe as to incapacitate the patient at the slightest contact, while in the second case, "detective work" was necessary in uncovering latex baby pants as the cause of dermatitis in a mother. Unsuccessful attempts were made to trace the offending ingredients in both cases, but this quest is difficult because of the complexity of synthetic rubber, certain rubber processing methods and unwillingness of the manufacturers to cooperate fully with investigators.

GENETICS OF XANTHOMA TUBEROSUM MULTIPLEX

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THE PRIMARY essential xanthomatoses have been divided by Thannhauser and Magendantz,¹ Montgomery² and others on the basis of the clinical picture and the fat content of the blood. The xanthoma tuberosum type with which this paper will concern itself is characterized by hypercholesteremia and a tendency to xanthomatous involvement of the skin, tendon tumors and, of much graver consequence, early cardiovascular disease.

Although the familial occurrence of this condition has been recognized by many observers³ since its description in 1851 by Addison and

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1 Thannhauser, S J, and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of Twenty-Two Cases, *Ann Int Med* **11** 1662, 1938. Thannhauser, S J. Lipoidoses. Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940.

2 Montgomery, H. Cutaneous Manifestations of Diseases of Lipoid Metabolism, *M Clin North America* **24** 1249, 1940.

3 (a) Montgomery² (b) Wilks, cited by Fagge, C H. Two Cases of Vitiligoidea Associated with Chronic Jaundice and Enlargement of the Liver, *Tr Path Soc London* **19** 434, 1868. (c) Mackenzie, S. Two Cases of Congenital Xanthelasma, *ibid* **33** 370, 1882. (d) Torok, L. De la nature des xanthomes (avec quelques remarques critiques sur la nature des tumeurs), *Ann de dermat et syph* **4** 1109, 1893. (e) Morichau-Beauchant and Bessonnet, R. Le xanthome hereditaire et familial, *Arch gen de med* **192** 2313, 1903. (f) Gossage, A M. The Inheritance of Certain Human Abnormalities, *Quart J Med* **1** 331, 1908. (g) Beeson, B B, and Albrecht, P G. Contribution to Study of Xanthoma Tuberosum, *Arch Dermat & Syph* **8** 695 (Nov) 1923. (h) Fasold, A. Studien über Vererbung von Hautkrankheiten VI. Xanthom (Cholesterosis cutis), *Arch f Rassen- u Gesellsch-Biol* **16** 54, 1924. (i) Grenaud M. Les xanthomes familiaux, Thesis, Paris, Jouve & Cie, 1927, *Monde med*, Paris **37** 725 (Aug 1) 1927.

Gull, Torok^{3d} was apparently the first to emphasize the hereditary nature of the disease. In the intervening years there have been several excellent reviews and reports touching on the genetic problems involved. The conclusions drawn have been of a conflicting nature, and the authors may be divided into several groups: (a) those⁴ who stated the belief that the mode of inheritance of xanthoma tuberosum multiplex was as a single dominant characteristic, (b) some⁵ who expressed the opinion that it was an irregular dominant characteristic, (c) others⁶ who stated that it was a recessive characteristic, (d) a group⁷ who expressed the opinion that the abnormality inherited was the disturbance in the cholesterol metabolism rather than in the xanthomatous deposits and (e) one⁸ who postulated two different genetic factors, one for the hypercholesteremia and the other for the deposits themselves.

For many years investigators⁹ have recognized the frequent association of xanthoma tuberosum with angina pectoris, coronary sclerosis, occlusive vascular disease of the extremities, arcus senilis or gallbladder disease. These observations have properly prompted several investi-

4 Torok^{3d} Muller, C. Angina Pectoris in Hereditary Xanthomatosis, *Arch Int Med* **64** 675 (Oct) 1939.

5 (a) Fasold^{3b} (b) Lane, G. C., and Goodman, J., Jr. Xanthoma Tuberosum. Report of Familial Occurrence with Probable Cardiac Lesions, *Arch Dermat & Syph* **32** 377 (Sept) 1935. (c) Lapowski, B. Familial Xanthoma Tuberosum Multiplex in Two Sisters, *ibid* **11** 701 (May) 1925.

6 Levin, E. A., and Sullivan, M. Familial Xanthoma, *Arch Dermat & Syph* **33** 967 (June) 1936. Thannhauser, S. J., and Schmidt, G. Lipins and Lipidoses, *Physiol Rev* **26** 275, 1946.

7 Lane and Goodman^{5b} Lapowski^{5c} Sperry, W. M., and Schick, B. Essential Xanthomatosis. Treatment with Cholesterol-Free Diet in Two Cases, *Am J Dis Child* **51** 1372 (June) 1936. Bloom, D., Kaufman, S. R., and Stevens, R. A. Hereditary Xanthomatosis, *Arch Dermat & Syph* **45** 1 (Jan) 1942. Svendsen, M. Are Supernormal Cholesterol Values in Serum Caused by a Dominantly Inherited Factor? Report of a Family Investigation of Thirty-Four Individuals, *Acta med Scandinav* **104** 235, 1940.

8 Polano, M. K. Ueber die Pathogenese der Cholesterosen der Haut, *Arch f Dermat u Syph* **174** 213, 1936.

9 Barker, N. W. Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, *Ann Int Med* **12** 1891, 1939. Chanutin, A., and Ludewig, S. Blood Lipid Studies in a Case of Xanthomatosis Associated with Hepatic Damage, *J Lab & Clin Med* **22** 903 1936. Weber, P. F. Cutaneous Xanthoma and "Xanthomatosis" of Other Parts of the Body—Pituitary Xanthomatosis—"Xanthomyelomata" of the Tendon Sheaths, etc., and "Cholesterolin Diathesis," *Brit J Dermat* **36** 335, 1924. Muller, C. Xanthomata, Hypercholesterinemia Angina Pectoris, *Acta med Scandinav*, 1938, supp 89, p 75. Klatskin, G. Familial Xanthomatosis and Arcus Senilis, *Internat Clin* **3** 13, 1941. Engelberg, H., and Newman, B. Z. Xanthomatosis. A Cause of Coronary Disease in Young Adults, *J A M A* **122** 1167 (Aug 21) 1943.

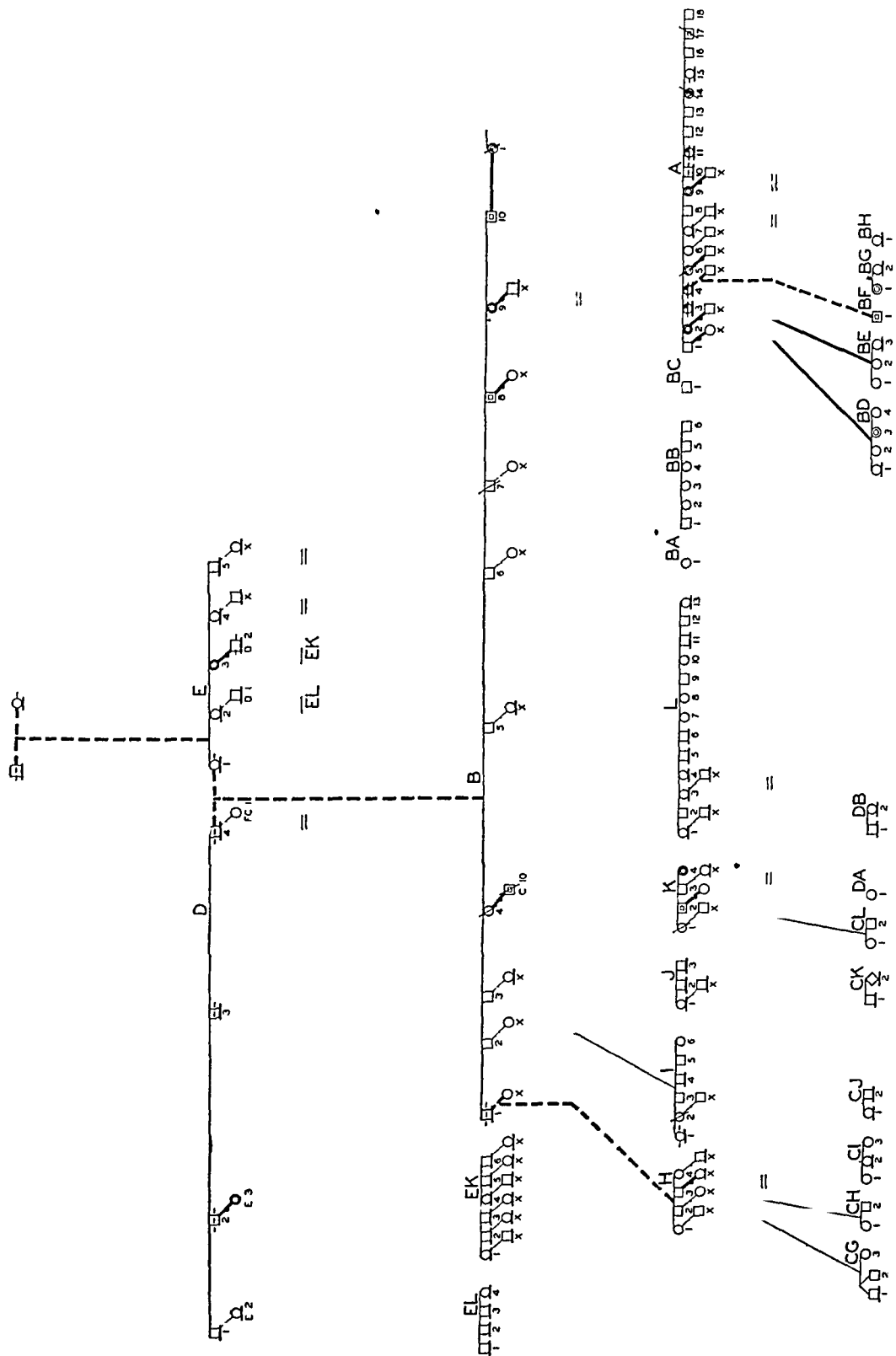
gators to suggest that near relatives of patients with xanthoma be examined for hypercholesteremia or other possible disturbances of lipid metabolism. Unfortunately, in most of the family cases thus far reported adequate physical, blood and other laboratory examinations on direct or collateral antecedents or descendants of affected persons have not been carried out.

In the present study a large kindred, comprising some 270 persons was investigated. In a recently presented study of this kindred we¹⁰ have described not only the historical information and physical observations in all available members of the family but blood lipid determinations and, in certain selected cases, observations on glucose tolerance, basal metabolism and dietary history.

The blood cholesterol values only are presented here and discussed from the point of view of their relationship to the inheritance of xanthoma tuberosum multiplex and their association with certain other clinical or anatomic abnormalities. Moreover, several additional hereditary characters were studied in an attempt to detect possible genetic linkages. The heretofore practical difficulties associated with the detection of "genetic carriers" of xanthoma tuberosum multiplex made this search for linkage with these more easily detectable and better understood genes of real importance. This group of characters include the ABO blood group, the MN blood type, the Rh positivity, the "secretor" factor, the taste reaction to phenyl-thiocarbamide and red-green color blindness. It was also hoped that these data will be of interest to those engaged in a statistical analysis of human pedigrees. Since the kindred was primarily studied for its lipid dyscrasia and the abnormalities associated therewith, the records on other factors will provide completely objective estimates of gene frequencies.

The drawing of the pedigree (fig 1) and the method used for designating persons was as follows: each sibship is lettered and each particular person designated by his or her sibship letter and a number. In general the number indicates position of birth, but because of condensation of the chart this is not true in all instances. Table 1 gives the age in years (as of March 1947) of all persons for whom data are available. Spouses are indicated by a small "x". In a few instances of double family marriages the spouse may have an independent designation, such as in the marriage of B-4 with C-11. Further information regarding these families may be obtained from the University of Michigan Heredity Clinic, where all records on this kindred (number 1064) are on file.

10 Wilkinson, C. F., Jr., Hand, E. A., and Fliegelman, M. T. Essential Familial Hypercholesterolemia, *Ann Int Med* 29: 671, 1948.



KEY

MALE	FEMALE	
□	○	NORMAL CHOLESTEROL
◻	◉	INCREASED BL CHOLESTEROL
◻	◉	BL CHOLESTEROL UNKNOWN
◻	◉	XANTHOMA TUBEROSUM
◻	◉	XANTHELASMA
◻	◉	CORONARY A A DISEASE
◻	◉	VALVULAR HEART DISEASE
◻	◉	E K G CHANGES
◻	◉	G B DISEASE
◻	◉	SUDDEN DEATH
◻	◉	DEATH

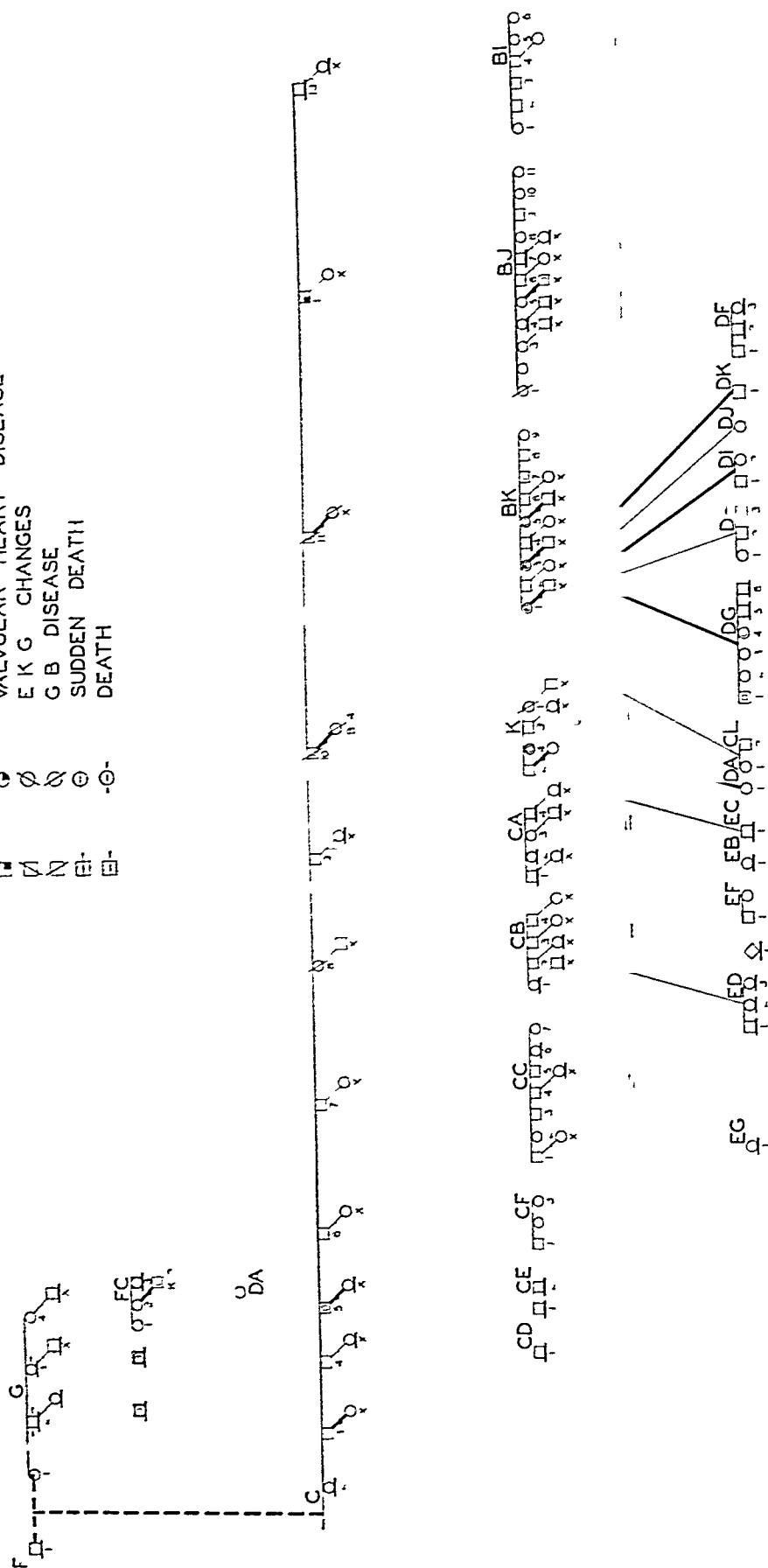


Fig 1—Pedigree of kindred exhibiting familial xanthoma tuberosum and essential hypercholesteremia (The figure is shown in two parts because of the limitation of page dimensions)

TABLE 1—Available Data for Subject in Pedigree (Fig 1) *

Subject	Sex	Age, Yr	Secretor Factor	Taste	Color Vision	Blood Types		Blood Cholesterol, Mg /100 Cc
A 1	M	30		T		O	MN	350
A 1X	F	26		T	Normal	O	MN	210
A 2	F	29				O	N	433
A 2X	M	32				A ₁	N	180
A 3	F	25 (d)						Pos
A 4	F	23 (d)						
A 4X	M	35				A ₁	MN	250
A 5	F	23	S	T	Normal	A ₂	M	335
A 5X	M	27	S	t		A ₂ B	MN	208
A 6	F	22	S	T	Normal	A ₂	M	213
A 6X	M	20-30						262
A 7	F	20						
A 8	M	19				A ₂	M	216
A 9	F	25		T	Normal	O	MN	325
A 9X	M	20-30						262
A 10	M	7 (d)						
A 11	F	14 (d)						
A 12	M	14	S	T	Normal	A ₂	MN	254
A 13	M	12	S	T	(RG CB)	A ₂	M	394
A 14	F	11	S	T	(RG CB)	A ₂	M	700
A 15	F	5/12 (d)						
A 16	M	8	S	T	Normal	A ₂	MN	185
A 17	M	3	S	t ?		A ₂	M	550
A 18	M	1	S	t		A ₂	MN	381
B 1	M	(d)						
B 1X	F	62				A ₁	MN	237
B 2	M	53				A ₂	M	194†
B 2X	F	52				B	MN	220
B 3	M	51						187
B 3X	F	49						
B 4	F	50	S	T	(RG CB)	A ₁ B	MN	216
B 5	M	47				A ₂	N	Neg
B 5X	F							
B 6	M	43				A ₁	N	Neg
B 6X	F	36				O	N	Pos
B 7	M	41				A ₂	MN	183
B 7X	F	35				A ₂	M	251
B 8	M	38				A ₁	MN	370
B 8X	F	36				O	M	150
B 9	F	46				A ₂	N	Pos
B 9X	M	58						
B 10	M	49		T	Normal	A ₂	MN	446
C 1	F	49		T	Normal	O	M	288†
C 2	F	41						
C 3	M	40				B	M	420
C 3X	F	42						
C 4	M	48				A ₁	M	182
C 4X	F	50						
C 5	M	44				A ₁	M	412
C 5X	F	42				A ₁	MN	
C 6	M	42				O	M	146
C 6X	F	42				A ₁	N	175
C 7	M	51				O	M	153
C 7X	F	49				O	MN	225
C 8	F	53				O	MN	196
C 8X	M	57				O	MN	222
C 9	M	56				O	MN	210
C 9X	F	(d)						
C 10	M	57	S	T	Normal	A ₁	M	320

TABLE 1—Available Data for Subject in Pedigree (Fig 1)*—Continued

Subject	Sex	Age, Yr	Secretor Factor	Taste	Color Vision	Blood Types		Blood Cholesterol, Mg/100 Cc
C 11	M	56		T	Normal	O	M	350
C 11X	F	59				A ₂	N	230
C 12	M	59				A ₁	M	248
C 12X	F	58				O	MN	175
C 13	M	(d)						
C 13X	F	59						
E 3	F	71				A ₁	N	Pos 315
G 1	F	80		T	Normal	O	M	161
G 4	F	77				O	MN	212
H 1	F	28				A ₁	M	166
H-1X	M	30				B	MN	200
H 2	M	30				A ₁ B	M	186
H 2X	F	28				A ₁	M	187
H 3	M	29				A ₁ B	N	Pos 312
H 3X	F							
H 4	F	31				A ₁	MN	196
H 4X	M	30				A ₁	MN	
I 1	F	4/12 (d)						
I 2	F	28				A ₁ B	MN	251
I 2X	M	28				A ₁	MN	220
I 1	M	17				A ₁	M	215
I 4	M	26				A ₁	MN	
I 5	M	25				A ₁	MN	205
I 6	F	22				A ₁ B	N	125
K 1	F	30	S	t	Normal	A ₁ B	MN	
K 1X	M	35		T	Normal	O	N	223
K 2	M	19	S	t	RG CB	A ₂	MN	248†
K 3	M	25	S	T	Normal	A ₁ B	N	140
K 3X	F	23	S	T	Normal	B	N	†
K-4	F	20	S	T	Normal	A ₁ B	MN	283
L-2	M	22				A ₂	N	Neg 237
L-7	F	10				O	N	Neg 158
L-8	F	7				O	N	Pos 166
L-9	M	7				A ₂	N	Pos 160
L-10	F	2				O	N	Pos 167
L-12	M	3				A ₁ B	N	Pos 200
L-13	F	13				A ₁	N	Neg
B 1 1	F	17				A ₁	N	Neg 210
BB 1	M	14				A ₂	MN	215
BB 2	F	13				A ₂	MN	251
BB 3	F	9				O	MN	251
BB 4	F	7				A ₂	M	220
BB 5	M	5				A ₂	MN	237
BB 6	M	4				A ₂	MN	
BC 1	M	10				O	MN	271
BD 2	F	6		T	Normal			190
BD 3	F	4		t		O	M	425
BD-4	F	3		t		O	M	187
BE 1	F	7				A ₂	N	Pos 187
BE 2	F	4				A ₁	N	Pos 237
BE 3	F	1/12						
BF 1	M	4				O	M	415
BG 1	F	4	S	t		A ₁	M	316
BG 2	F	1						
BI 1	F	32				O	MN	147
BI 2	M	28				A ₁	MN	205
BI 3	M	25				O	MN	135
BI 4	M	29				O	MN	152
BI 4X	F	20-30						187

TABLE 1—Available Data for Subject in Pedigree (Fig 1)*—Continued

Subject	Sex	Age, Yr	Secretor Factor	Taste	Color Vision	Blood Types		Blood Cholesterol, Mg /100 Cc
BI 5	F	19				O	MN	135
BI 6	F	23				A ₁	M	275
BJ 1	F	34				O	M	169†
BJ 2	F	32				A ₁ B	M	141†
BJ 3	F	31		t	Normal	A ₁ B	MN	200
BJ 3X	M	33				O	N	
BJ 4	F	29				B	MN	
BJ 4X	M	30				O	MN	
BJ 5	F	27				A ₁	MN	225
BJ 5X	M	29				O	M	236
BJ 6	M	25				A ₁	MN	133†
BJ 6X	F	20				A ₂ B	M	203
BJ 7	M	24						
BJ 7X	F	18						
BJ 8	F	23				O	M	151†
BJ 9	M	21				A ₁	MN	188
BJ 10	F	18				O	MN	119†
BJ 11	F	16				O	MN	116†
BK 1	F	34	S	T	Normal	A ₁	MN	430
BK 1X	M	34		T	RG CB	A ₁ B	N	163
BK 2	M	32	S	T	Normal	A ₁	MN	210
BK 2X	F	27	S			A ₁	MN	152
BK 3	F	30	S	T	Normal	A ₁	MN	433
BK 3X	M	32						175
BK 4	M	28		T	Normal	O	MN	
BK 4X	F	22		T	Normal	O	MN	227
BK 5	F	25	S	T	Normal	A ₁	MN	333
BK 6	M	23		T	Normal	O	MN	170
BK 6X	F	21		T	Normal			204
BK 7	M	22	S	T	Normal	A ₂	MN	337
BK 8	M	20	S	T	Normal	A ₁	MN	205
BK 9	F	19	S	T	Normal	A ₁	MN	188
CA 1	M	30						
CA 1X	F	26				O	MN	
CA 2	F	24						
CA 3	F	21				O	MN	140
CA 4	M	28				O	MN	
CA 4X	F					O	M	
CB 1	F	30						
CB 1X	M	33						
CB 2	M	27				O	M	215
CB 2X	F	23						
CB 3	M	26				O	M	210
CB 3X	F	21						200
CB 4	M	29				O	M	193†
CB 4X	F	23				O	MN	175
CC 1	M	29				O	MN	175
CC 1X	F	25				B	N	155
CC 2	F	26				O	MN	165
CC 3	M	24				O	M	169†
CC 4	M	22				B	MN	183
CC 4X	F	20 30				O	MN	
CC 5	F	19				O	MN	167
CC 6	F	3 (d)						
CC 7	F	10				O	MN	170
CE 1	M	8				A ₁	MN	
CE 2	M	1						
CF 1	M	12				O	MN	182
CF 2	F	15				O	MN	250

TABLE 1—Available Data for Subject in Pedigree (Fig 1)¹—Continued

Subject	Sex	Age, Yr	Secretor Factor	Taste	Color Vision	Blood Types ²		Blood Cholesterol, Mg/100 Cc
CF-3	F	3				A ₁	MN	175
CG 1	M	3				O	M	
CG 2	M	3				O	MN	170
CG 3	F	5						170
CH-1	F	6				A ₁	MN	200
CH-2	M	2				A ₁ B	MN	187
CI-1	F	5				O	MN	200
CI-2	F	1				A ₁	MN	
CI 3	F	8				O	MN	153
CJ 1	F	6				A ₁	MN	
CJ-2	M	1/12						
CL-1	F	11	S	T	Normal	A ₁	MN	187
CL-2	M	7	S	T	Normal	A ₁	M	250
DA-1	F	2	S			A ₂	MN	175
DF 1	M	5				A ₁	N	183
DF 2	M	4				A ₁	MN	
DF 3	F	3				O	MN	
DG 1	M	9	S	T	Normal	A ₁	MN	406
DG 2	F	7	S	T	Normal	A ₂ B	M	196
DG 3	F	6	S	T	Normal	A ₁	MN	196
DG-4	F	5	s	T	Normal	A ₁ B	MN	341
DG 5	M	2				A ₂ B	MN	
DG-6	M	1						
DH-1	F	7				A ₁	MN	153
DH-2	M	6		T	Normal	A ₁	N	160
DH 3	M	3	S	T		A ₁	MN	160
DI 1	M	2	S	T		A ₂	MN	152
DI 2	F	5				O	M	205
DJ-1	F	3		t		O	MN	142†
DK 1	M	3		T		A ₁	M	165
EB-1	F	3				A ₁	M	
EC 1	M	3				B	MN	
EF-1	M	3						203
EF 3	F	6				O	MN	153
EG 1	F	2 (d)				O	N	
FC 1	F	57				A ₁	M	237
FC 2	F	48		T	Normal	O	MN	196

* S is secretor, s is nonsecretor, T is taster, t is nontaster, RG CB is red green color blindness, (RG CB) means retest was indicated, because of possible inability to read numbers, low mentality or inattention, and (d) means the subject died at the stated age prior to March 1947 or during the course of study

† Schoenheimer Sperry method

‡ The subject was pregnant when the study was made

METHODS OF STUDY

1 *Blood Lipid Tests* A modified Bloor¹¹ method for determining blood cholesterol was used in the initial survey because of the large number of persons involved. The method was later changed to the more accurate and time-consuming Schoenheimer-Sperry¹² technic,

11 Todd, J. C., and Sanford, A. H. *Clinical Diagnosis*, ed. 10, Philadelphia, W. B. Saunders Company, 1943, p. 380

12 Schoenheimer, R., and Sperry, W. M. *Micromethod for Determining Free and Combined Cholesterol*, *J. Biol. Chem.* **106**: 745, 1934

when certain metabolic studies, which are still being carried out, were started. Consequently, the few values determined by the latter method are designated in table 1 by a dagger.

Figure 2 shows the frequency distribution of blood cholesterol levels. Rather than presenting the normal or bell-shaped curve the curve appears to be bimodal, as might be expected if the group were comprised of two genetically different types. The minimal point between the two groups is in the neighborhood of 280 mg per hundred cubic centimeters, the value adopted as our criterion for hypercholesteremia. The appropriateness of this level is perhaps further substantiated by the fact that the 30 relatives classified as hypercholesteremic show levels in agreement with the predicted genetic pattern of transmission, as will be discussed later.

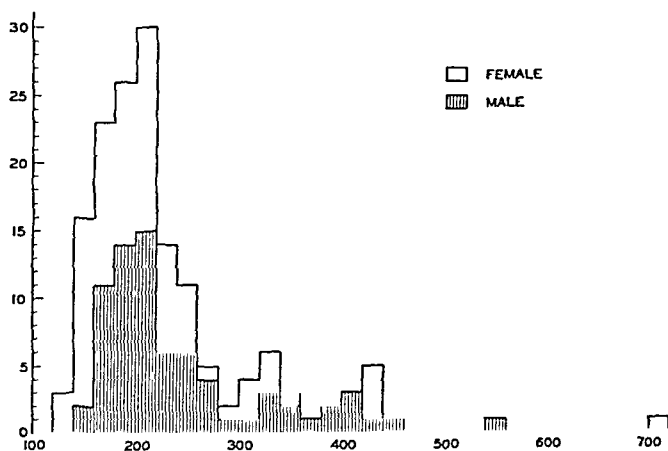


Fig. 2—Frequency distribution curve of blood cholesterol levels of 159 members of kindred. The vertical column of figures shows the number of subjects and the horizontal line of figures shows the blood cholesterol values in milligrams per hundred cubic centimeters.

We considered 210 mg per hundred cubic centimeters by the Schoenheimer-Sperry method as our hypercholesteremic level, although they have all been expressed in Bloor method figures in figure 2.

A further point in substantiation of these values lies in the consideration of the 3 persons called normocholesteremic by us (B-5, BI-6, BC-1) whose blood cholesterol values exceeded 260 mg per hundred cubic centimeters by the Bloor or 200 mg per hundred cubic centimeters by the Schoenheimer-Sperry technic. B-5 is the father of many children. The 5 seen by us all had definitely normal blood cholesterol levels. BI-6 is 1 of 6 children, the 5 others having normal blood cholesterol levels. BC-1 is the only child of a hypercholesteremic father and a normocholesteremic mother, and so his chances of being one or the other are about equal.

2 *ABO, MN and Rh Blood Classification* A specimen of a few drops of the venous blood drawn for the lipid studies was refrigerated as saline suspensions and tested within forty-eight hours of collection. The tests for the presence of agglutinogens A₁, A₂, B, M, N and Rh were made with standard testing serums and 2 per cent cell suspensions. In each series of tests control bloods of the ABO MN and Rh classifications were used.

3 *Secretor Test* It has been known for many years that the saliva (as well as other body fluids) of certain persons of groups A, B and AB contained the corresponding antigens in concentrations that are higher than the red blood cells, while the saliva of other persons may contain virtually none of these antigens. While the mechanism of this condition is obscure it is inherited as a single gene difference, the secretor condition being dominant to the nonsecretor. Furthermore, the difference as shown by Schiff and Sasaki¹³ was also found in group O persons. The method of performing this test has been previously described by Cotterman and Falls¹⁴.

4 *Taste Test* While the determination of "tasters" and "non-tasters" of phenyl-thiocarbamide is undoubtedly best done with serial dilutions of a saturated solution thereof, in this study small quantities of the powdered crystals were placed on the tongue. Subjects were asked to describe the taste. There were no control test substances employed and in some instances there were children tested who were perhaps too young for reliable diagnosis. Moreover, it was usually necessary to test a subject in circumstances which allowed that person to learn the reactions of those about him who were being tested at the same time. Nevertheless, the results appear to be sufficiently accurate for linkage detection.

5 *Color Blindness* The subjects were tested for color blindness with the pseudoisochromatic charts of Ishihara and Stilling.

Table 1 presents the data on this kindred that is presently available.

COMMENT

The original patients for our pedigree are the sister and brother A-14 and A-17, both suffering from xanthoma tuberosum multiplex. In a preliminary visit to their home it was not only suggested to us that there was a definite pattern of inheritance of the abnormality, but we discovered that 2 older sisters (A-3, A-4), now no longer

13 Schiff F, and Sasaki, H. Ueber die Vererbung des serologischen Ausscheidungstypus, Ztschr f Immunitätsforsch u exper Therap **77** 129, 1932.

14 Cotterman, C W, and Falls, H F. Genetic Studies on Ectopia Lentis, Ann Eugenics **12** 158, 1944.

living, had also suffered from this same syndrome and had been studied by Curtis, Wile, Duemling and Eckstein¹⁵ at the University of Michigan. Their hospital records were available to us, and, while blood cholesterol values had not been reported, the photographs and other clinical and pathologic data make certain the diagnosis of xanthoma tuberosum multiplex. Another sister (A-11), now dead, was reliably reported to have had xanthoma tuberosum lesions.

MALE	FEMALE	
□	○	NORMAL CHOLESTEROL
◻	◎	INCREASED BL CHOLESTEROL
◻	◌	BL CHOLESTEROL UNKNOWN
◻	◌	XANTHOMA TUBEROSUM
◻	◌	XANTHELASMA
◻	◌	CORONARY A A DISEASE
◻	◌	VALVULAR HEART DISEASE
◻	◌	E K G CHANGES
◻	◌	G B DISEASE
◻	○	SUDDEN DEATH
◻	◌	DEATH

Fig 3—Enlarged reproduction of key taken from figure 1

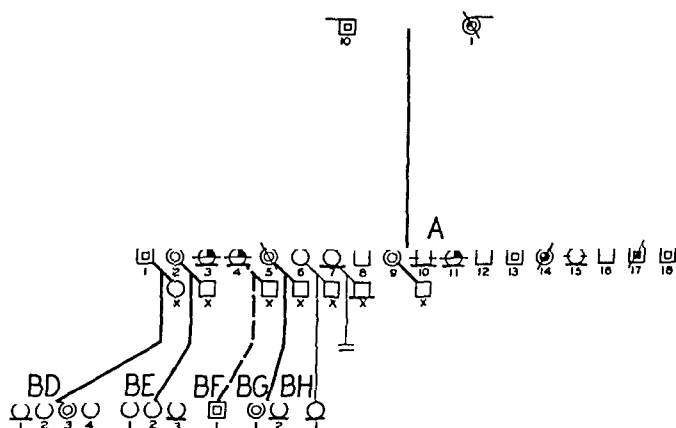


Fig 4—Sibships A and BF

This kindred contains four distinctly different types of matings: a hypercholesteremic person with a hypercholesteremic one, a nor-

15 (a) Curtis, A C, Wile, U J, and Eckstein, H C. The Involvement of Cutaneous Xanthomata Caused by Diets Low in Calories, *J Clin Investigation* **7** 249, 1929. (b) Wile, U J, and Duemling, W W. Familial Xanthoma, *Arch Dermat & Syph* **21** 642 (April) 1930. (c) Wile, U J, Eckstein, H C, and Curtis, A C. Lipid Studies in Xanthoma. Further Contribution, *ibid* **20** 489 (March) 1929.

mal person with one suffering from xanthoma tuberosum multiplex, a normal person with a normal one and a normal person with a hypercholesteremic one. The observations in offspring of these matings have caused us to consider xanthoma tuberosum multiplex the homozygous abnormal state, the heterozygous state producing hypercholesteremia alone.

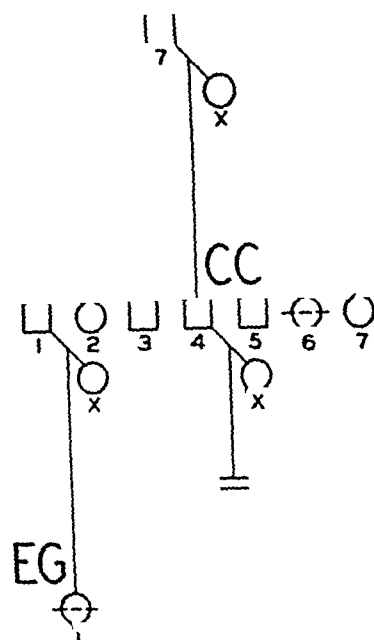


Fig 5—Sibship CC

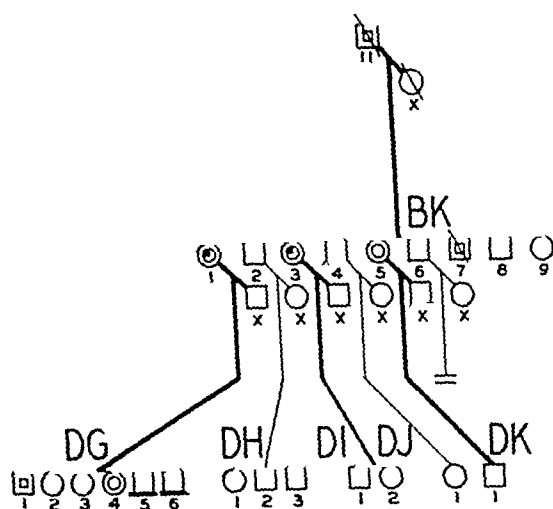


Fig 6—Sibship BK

The various matings of these persons with their resultant mendelian ratios are well illustrated. The symbols for the various known abnormalities in these persons, enlarged from figure 1, is shown in figure 3. Sibship A, (fig 4) for example, is the result of the mating of two heterozygotes (C-1 and B-10) who had increased blood cholesterol values. The heavy black line connecting and descending vertically

from them denotes the transmission of this abnormal trait through this mating. The expected ratio of 1 homozygous abnormal person, 2 heterozygous persons and 1 homozygous normal person is approximated. Actually, of the 18 children in this sibship 5 had xanthoma tuberosum and/or tendinosum (A-3, A-4, A-11, A-14, A-17), 6 had elevated blood cholesterol levels without cutaneous lesions (A-1, A-2, A-5, A-9, A-13, A-18) and 4 had normal blood cholesterol values (A-6, A-8, A-12, A-16). Three are reported not to have had cutaneous lesions (A-7, A-10, A-15), but their cholesterol levels are not known.

In the union of A-4, who had xanthoma tuberosum, and A-4_x (fig 4), whose blood cholesterol was normal, the only possible type of offspring must be the hypercholesteremic heterozygote, if our thesis is correct. The only child (BF-1) showed the expected increased

TABLE 2—Numbers of Affected and Normal Children Among Offspring of Various Matings

Matings	Number of Matings	Elevated Blood Cholesterol Level	Normal Blood Cholesterol Level	Unexamined
Heterozygote X Heterozygote	{	Observed— 8	Observed— 4	6
Heterozygote		Expected— 9	Expected— 3	
Heterozygote X Normal	{	Observed—11	Observed—13	5
Normal		Expected—12	Expected—12	
Normal X Normal	{	Observed— 0	Observed—41	7
Normal		Expected— 0	Expected—41	
Homozygous abnormal X Normal	{	Observed— 1	Observed— 0	0
Normal		Expected— 1	Expected— 0	

blood cholesterol value but no cutaneous lesions at the age of 3. (The heavy broken line indicates the anticipated transmission of the abnormal trait since this person (A-4) had been studied by Curtis and his co-workers^{15a} and not by us.)

The elevated blood cholesterol levels are transmitted to the succeeding generation by other members of sibship A, as indicated by the heavy black lines shown in figure 4.

Normal offspring would, of course, be expected to result from the mating of 2 normal parents (C-7 and C-7_x). Sibship CC (fig 5) illustrates this. It is comprised of 6 living persons who were normal on physical examination, all of whom had normal blood cholesterol levels, and 1 dead (CC-6), whose blood cholesterol level was not determined.

The progeny resulting from the union of a normal person (C-11_x) with a heterozygote (C-11) are found in the expected ratio of 1 normal person to 1 heterozygote, as can be seen in sibship BK (fig 6).

Here none of the 8 children examined had cutaneous lesions, but 4 (BK-2, BK-6, BK-8, BK-9) had normal and four (BK-1, BK-3, BK-5, BK-7) had elevated blood cholesterol levels. One (BK-4) was not seen by us.

Again, where there are enough offspring in the next generation of this family line, the hypercholesteremia is transmitted (as indicated by the heavy black lines) in the usual ratio.

More detailed reference to the pedigree will reveal other illustrations of some of these types of matings, and table 2 shows the total observed and expected numbers of affected and normal children among the offspring of the various types of matings when both parents had been examined and their blood cholesterol levels determined. There were two possible matings (homozygous abnormal with homozygous abnormal and homozygous abnormal with heterozygote) that were not

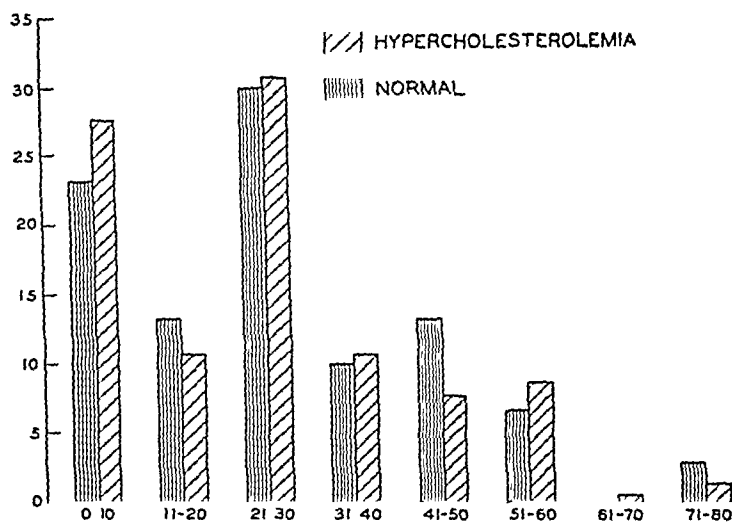


Fig 7—Percentage distribution by age of 30 hypercholesteremic and 129 normocholesteremic persons. The horizontal row of figures shows the age in years, and the vertical column of figures shows the percentage of the group.

found in this kindred. It should also be noted that both the homozygous abnormal and heterozygous state of this condition may be detected very early in life by appropriate blood and physical examinations. Moreover, even at an early age the homozygous person with two abnormal genes has a higher blood cholesterol level (over 500 mg per hundred cubic centimeters in this kindred), while the heterozygous person tends to have a more moderate elevation (283 to 416 mg per hundred cubic centimeters).

While the kindred studied is composed of some 270 persons, only 159 will be included in our statistical studies because only this number was studied sufficiently to rule out other common causes of hypercholesteremia (nephrotic syndrome, diabetes, hypothyroidism, pregnancy and hepatic disease) and included all cooperative and available

members of the kindred. Of these 159, 30 had elevated blood cholesterol levels and 129 had normal levels.

The age incidence of the normal and abnormal blood cholesterol level groups is shown in figure 7.

Many investigators⁹ have associated certain clinical and/or anatomic abnormalities with xanthomatous deposits in the skin, and the relative frequency of these complications in this kindred is shown in table 3.

Two of the hypercholesteremic groups studied by us had xanthoma tuberosum and/or tendinosum, while 3 others, as discussed elsewhere, also showed xanthomatous lesions of the skin.

Xanthelasma was found in 3 subjects in the group with elevated cholesterol levels and in 1 subject in the group with normal blood cholesterol levels.

TABLE 3—*Relative Frequency of Clinical and/or Anatomic Abnormalities*

	Hypercholesteremia		Normocholesteremia	
	Number of Subjects (Total 30)	Percentage	Number of Subjects (Total 129)	Percentage
Xanthoma tuberosum	2	6.6	0	0.0
Xanthoma tendinosa				
Xanthelasma	3	10.0	1	0.8
Arcus juvenilis/senilis	0	0.0	1	0.8
Angina pectoris	1	3.3	1	0.8
Xanthomatous valvular heart disease	2	6.6	0	0.0
Gallbladder disease				
Clinical story	5	17.0	7	5.4
Roentgenogram taken	5	0.0	4	0.0
Roentgen observation positive	2	6.6	1	0.8
Hepatomegaly	5	17.0	3	2.3

Only 1 case of arcus senilis was found, and it occurred in a subject with a normal cholesterol level. However, it should be emphasized that no slit lamp examinations were performed.

No cases of myocardial infarction were found by us, but, since A-3, A-4 and A-11 all died suddenly and since they all had xanthoma tuberosum, it may well be suspected.

Both A-14 and A-17 had valvular heart disease, and, since there was no history of chorea, scarlet fever, diphtheria or rheumatic fever, it seems justifiable to assume that these valvular defects were due to xanthomatous deposits. A detailed analysis of the electrocardiographic observations and a cardiac evaluation of this kindred will be presented elsewhere.

A clinical history of gallbladder disease was found for 5 of the hypercholesteremic group and 7 of the normocholesteremic group, while 5 of the former group showed hepatomegaly and only 3 of the latter group demonstrated this abnormality.

No cases of biliary cirrhosis were found.

In the group of 30 persons with elevated cholesterol levels there were exactly 15 of each sex

A review of the genetic factors studied reveals that the ABO, MN and Rh blood groupings were inherited in the usual fashion. Two discrepancies were found. Both BJ-2 and BJ-3 were recorded as type A_1B persons and were the offspring of C-12, who was type A, and C-12_x, who was type O. Progeny of such a mating could not possibly be type A_1B , but since, from the blood cholesterol point of view, C-12, C-12_x and all their offspring had normal values this observation did not invalidate our primary thesis.

Both the secretor factor and the ability to taste phenyl-thiocarbamide were found to be inherited in this kindred in the usual fashion.

Red-green color blindness of the deuteranopia type was found in one sibship (K) of those tested. This anomaly could not be traced further by either testing or hearsay evidence.

No complete linkage was found between blood cholesterol levels and any of the genetic factors studied, but a final analysis of them has not been made.

In the light of these data we feel that the metabolic disorder manifested by an increased blood cholesterol value, designated and discussed elsewhere by us as "essential familial hypercholesterolemia,"¹⁰ is transmitted as if due to a single abnormal gene which is incompletely dominant to its normal allele.

The three possible combinations of these genes comprise (a) the homozygous normal person with two normal genes, (b) the heterozygote who has one abnormal gene and hypercholesterolemia and (c) the homozygous abnormal person with two pathologic genes and showing not only hypercholesterolemia but xanthoma tuberosum multiplex as well and, in many instances, cardiovascular system damage and other abnormalities.

This mode of inheritance, when the heterozygous person with one abnormal gene is distinguishable from the homozygote affected with two abnormal genes, is called incomplete or intermediate dominance. Obviously, the homozygote affected person will transmit an abnormal gene to all of his or her offspring, but the ability to recognize the heterozygous state is of the greatest practical importance, for it is these persons who are the genetic carriers of the abnormal gene. (In a broad sense a "genetic carrier" is one who may transmit an inherited disease or produce more carriers in progeny without actually showing the commonly accepted observations of the full blown disease himself¹⁶.)

¹⁶ Neel, J. V. The Clinical Detection of the Genetic Carriers of Inherited Disease, *Medicine* 26:115, 1947.

The discovery of this method for the detection of the heterozygous carriers is a major step forward in the early diagnosis of this inherited disease. It is certainly a prerequisite for its genetic control. That such control is indicated is indisputable.

SUMMARY AND CONCLUSIONS

Essential familial hypercholesteremia is transmitted as an incomplete dominant trait. Xanthoma tuberosum multiplex represents the homozygous state for an inherited factor which when heterozygous produces only hypercholesteremia. The upper limit of normality for blood cholesterol levels has been established statistically and genetically. Neither sex nor age influence the occurrence of hypercholesteremia. The greater incidence of certain pathologic conditions in the abnormal group as compared to the normal group is illustrated. It is now possible to predict the matings which may be expected to produce a person with xanthoma tuberosum multiplex: the matings of 2 homozygous abnormal persons, or of a homozygous abnormal with a heterozygote or that of 2 heterozygotes.

ABSTRACT OF DISCUSSION

DR HAMILTON MONTGOMERY, Rochester, Minn. Dr Fliegelman and his associates have done an excellent job on the genetics of xanthoma. The paper is concise and should be read word for word and then reread. I am glad to see this paper come from Ann Arbor because it amplifies the facts on 2 cases of juvenile xanthoma in the same family reported by Drs Wile, Curtis and Eckstein in *THE ARCHIVES* in 1929. The studies of Dr Fliegelman and his associates confirm and surpass the studies of genetics reported in an excellent paper some years ago by Muller (*Arch Int Med* 64: 675-700 [Oct.] 1939). I wish to emphasize that practically all patients with xanthoma tuberosum have hyperlipemia and hypercholesteremia and that in 40 per cent or more of the cases there is associated cardiovascular disease in the form of angina pectoris and coronary sclerosis or intermittent claudication and arteriosclerosis obliterans. I would like to ask Dr Fliegelman why children more frequently have lesions of the mitral valve than elsewhere and why in adults, when the heart is affected, the coronary arteries are involved. It is important to recognize that xanthoma tuberosum often occurs as a familial disease and that angina pectoris occurs at an earlier age in adults with xanthoma tuberosum, usually in the early forties, than in the general adult population, in which the highest incidence is in the fifties and sixties. In a given family one member may have hypercholesteremia without evidence of coronary disease for a period of many years, another may have xanthoma tuberosum, hypercholesteremia and coronary disease and in others cutaneous manifestations may be limited to small xanthelasma of the eyelids, yet with systemic xanthomatosis. In about 15 per cent of the cases of xanthoma tuberosum, there is evidence of hepatic involvement, usually in the form of xanthomatous biliary cirrhosis. If patients with xanthoma tuberosum associated with cardiovascular disease are put on a rigid, animal fat-free diet plus a supplement of necessary vitamins, the early cutaneous lesions will involute, but more important the blood plasma lipids can often be returned to normal and further damage to the cardiovascular system can be minimized. I know of a former student who

has outlived by at least ten years his anticipated life expectancy by adhering to such a diet. In xanthoma limited to the eyelids, about 50 per cent of the patients have hypercholesteremia, and of the 50 per cent about half have evidence of cardiovascular disease, hence the presence even of xanthelasma calls for determination of blood plasma lipids. The dermatologist, therefore, can be of assistance to the internist, because in xanthoma tuberosum and xanthelasma he can anticipate that certain patients will have coronary disease because of the cutaneous manifestations and because of the hypercholesteremia and hyperlipemia.

DR JOHN GARB, New York. Dr Fliegelman and his associates confirm the theory recognized by most investigators that hypercholesteremia is the basic underlying disturbance in the inheritance of xanthoma tuberosum. As far as the large family which they studied is concerned they have proved that hypercholesteremia with or without xanthelasma is due to one defective gene, present in a heterozygotic person, while a homozygote manifests not only hypercholesteremia but also xanthomatosis of the skin with or without cardiovascular involvement. This genetic behavior of the syndrome would be comparable to that of brachydactyly which is believed to reveal itself in the homozygotic state in a severer form than in the heterozygotic state. Although the authors' contention is borne out in their case pedigrees, studies in this one family may not be sufficient to prove the general validity of this mode of transmission in all cases of xanthoma tuberosum. Additional families and more cases would be required to consider their concept as universally applicable. Dr David Bloom and his associates of New York Skin and Cancer Unit conceived the hypothesis that hypercholesteremia, cutaneous xanthomatosis and cardiovascular involvement with or without sudden death, alone or combined, constitute a syndrome which may be manifested fully or partially—comparable to the syndrome of adenoma sebaceum and tuberous sclerosis. They stated the belief that even the expression of the full syndrome does not require a homozygotic person and the presence of only one defective gene is sufficient. According to this opinion xanthomatosis as a dominant disease may manifest itself in the heterozygotic state as hypercholesteremia alone or associated with xanthoma tuberosum with or without cardiovascular disease, or as hypercholesteremia with cardiovascular complication without cutaneous xanthomatosis.

The general validity of the concept of Dr Fliegelman and his associates that the homozygote has severer clinical manifestations than the heterozygote is contradicted in the literature by studies of at least one family. In this unusual family reported by Bloom, Kaufman and Stevens (*Hereditary Xanthomatosis*, *ARCH DERMAT & SYPH* 45:1 [Jan] 1942), the 5 siblings, even though they had the full syndrome of hypercholesteremia, xanthoma tuberosum and cardiovascular disease, with sudden death in 4, could not have been homozygotes because the mother was normal and the father had hypercholesteremia alone and, according to Dr Fliegelman, could be considered only a heterozygote.

I agree with Dr Fliegelman regarding the importance of blood cholesterol studies in relation to cases of xanthoma tuberosum. It is fortunate that in this syndrome the elevated blood cholesterol level is a warning of the disease. Dietary measures of low cholesterol and low fat with perhaps administration of lipocain (pancreatic extract) or a lipotropic substance, such as lecithin, and routine examinations carried out regularly and periodically for life may possibly prevent xanthomatous lesions with serious complications, especially in the cardiovascular apparatus. May I suggest that a routine blood cholesterol test, like a Wassermann test, would be valuable in clinics and in private practice? It may reveal many cases in which there are elevated blood cholesterol levels and other stigmas of disturbed

lipid metabolism Too little attention has been paid to this important branch of science, which, if applied to research, would aid in solving many obscure problems and might reveal the basis of metabolic and other disorders affecting the heart, vascular tree, viscera and skin Drs Flegelman, Wilkinson and Hand must be congratulated for their vast and painstaking study of such a vital inherited disease and for the stimulation that it ought to give generally and particularly to the investigation of genetics in the field of dermatology

DR DAVID ADLERSBERG, New York I wish to speak from the point of view of the internist interested in this syndrome because of the well established association of xanthomatosis, coronary artery disease and hypercholesteremia A study of families with xanthomatosis by Drs Boas, Parets and myself revealed many interesting facts First, this disorder is not so rare as we originally thought In the course of the first few months, we had examined and reported on 55 members belonging to seven families, as well as 9 additional patients whose families were not available for study The study being at present prepared for publication includes thirty-two families and reveals that only a small group of the members manifest the full syndrome, namely, xanthoma tuberosum or tendinosum, xanthelasma, arcus juvenilis, atherosclerosis of the coronary arteries and hypercholesteremia In the other subjects, the lesions may be found in various combinations Some of the subjects present only the cutaneous lesions and hypercholesteremia and others only coronary artery disease with or without xanthomatosis and with or without arcus juvenilis The most constant feature is the elevation of the blood cholesterol level, which may be found, not infrequently, even among children of these families We consider, at present, only levels above 300 mg per hundred cubic centimeters as abnormal The practical importance of this disorder may be illustrated by the following case A woman of 43 was admitted to the hospital with coronary thrombosis She had xanthelasma of the eyelids and a blood cholesterol level of 525 mg per hundred cubic centimeters She survived the attack but died, at home, a few months later from another coronary occlusion Two brothers and one sister of the patient had blood cholesterol levels ranging from 450 to 560 mg Two other brothers had died at the ages of 31 and 37 of coronary artery disease A complete autopsy report of the younger brother was available and revealed severe atherosclerosis of the coronary arteries, his blood cholesterol was not studied, and it was not known, at that time, that he belonged to a hypercholesteremic family It was only fifteen years later, when his sister was observed at the hospital and the whole family studied, that the true nature of the disorder became apparent Studies of young persons with coronary artery disease has unmasked many similar instances of hereditary hypercholesteremia

We had the impression that families with xanthoma represent only the extremes of disturbed lipid metabolism and that many persons with seemingly uncomplicated coronary artery disease may fall into a similar pattern A study of 122 consecutive patients with proved coronary artery disease below the age of 50 confirmed this impression In 58 per cent of these patients the serum cholesterol level was elevated over 300 mg per hundred cubic centimeters Arcus juvenilis was exhibited by 22, xanthelasma by 12 and xanthoma by 3 In one third of fifty families of this group was hypercholesteremia found in all or most of the siblings, and, in addition, in nine more families one half of the siblings showed hypercholesteremia

As far as therapy is concerned, a cholesterol-free diet with the addition of lecithin deserves a trial The results are not too satisfactory, although some persons show a striking drop in the serum cholesterol level The role of dietary

cholesterol in hypercholesteremia is not established. We definitely know that cholesterol can be synthesized in the body, e g, from acetic acid. Since hypercholesteremia reflects a metabolic disturbance, efforts are justified to modify its influence on the vascular system much as one attempts to obviate the complications of diabetes by diet and insulin therapy. A pharmacologic counterpart to insulin for the treatment of hypercholesteremia is not beyond the realm of possibility but is not available at present.

DR. DAVID KAHN, Lansing, Mich. In predicting the occurrence of xanthoma tuberosum from the blood cholesterol value, a word of caution may be in order. Several years ago, in studying a group of psoriatic patients, my associates and I noted great variations in blood cholesterol values, when determined at weekly or biweekly intervals over a period, in some cases, of a year or longer. It is therefore advisable that one do a number of cholesterol determinations in each patient before coming to a final decision.

DR. CHARLES F WILKINSON, Ann Arbor, Mich. I stated in San Francisco, at the American College of Physicians, several weeks ago, that we also found coronary lesions in the younger subjects. One girl was reported who had had angina pectoris since the age of 9. In answer to Dr Garb's justifiable criticism that only one family had been reported, I may add that three additional families, in which xanthoma tuberosum was present, have also been studied in detail. These studies will be the subject of two additional papers, one by Dr Hand and myself and one by Colonel Fancher and myself. In addition, six other families with essential familial hypercholesteremia, but in which xanthoma tuberosum did not exist, have been studied in great detail. None of these patients have xanthoma as a result of the marriage when one parent had normocholesteremia.

With regard to the paper referred to by Bloom and his associates, the cholesterol was reported to be normal in the mother. However, no values were given. One thing that we could not explain is that the mother was designated with a question mark in the original paper. It would seem there was only one determination of the blood cholesterol, which was not reported, and, for one reason or another, the results were questionable. It was also reported that half of the siblings were hypercholesteremic. In answer to Dr Aldersberg, we agree that this is not an uncommon disease. We are limited in Ann Arbor in the number of persons we can study by our laboratory facilities. We found families in the department of internal medicine, which is not an unusually large staff. In our experience, arcus juvenilis is much more diagnostic for essential familial hypercholesteremia than arcus senilis. We feel that a better term is heterozygote abnormal, which Dr Fliegelman used.

I do not feel that this is the proper place to discuss the therapy, which we will make the subject of a later paper and which we have been working on for about a year and a half. We agree with a number of Dr Adlersberg's published reports, and we have not been quite in agreement with some others. I might add that we did from three to fifteen cholesterol tests for each subject.

EOSINOPHILIC GRANULOMA OF THE SKIN

Report of Three Cases

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AND

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EOSINOPHILIC granuloma of the skin is a new and not yet well defined disease entity. Occasional case reports under this diagnosis have appeared in the European literature since 1937. In the United States the disease received little attention until 1946. Since then, however, five papers on this subject have been published,¹ among them one from Boston.^{1d} Nineteen cases in which the disease was diagnosed as eosinophilic granuloma of the skin are now recorded in the literature.

Three additional cases have recently been seen in Boston. The appearance in these cases, clinically as well as histologically, was almost identical with that in the first case reported from Boston.^{1d} In fact, the clinical features of these 4 cases were so characteristic that in 1 instance (case 2) the diagnosis was made before biopsy.

REPORT OF CASES

CASE 1—A 52 year old man first noticed in 1942 a small asymptomatic purplish lesion in the left preauricular region. The lesion slowly increased in size. In 1943 two similar lesions appeared, one in the left zygomatic and the other in the left infraorbital region. In 1946, a fourth lesion developed just below the infraorbital one.

On examination, in October 1946, the patient presented four sharply demarcated, purplish, slightly elevated plaques. The infiltrate in the plaques felt soft,

From the Departments of Dermatology, Massachusetts General Hospital and Boston City Hospital.

1 (a) Buley, H M. Eosinophilic Granuloma of the Skin, *J Invest Dermat* 7 291, 1946. (b) Weidman, F D. The "Eosinophilic Granulomas" of the Skin, *Arch Dermat & Syph* 55 155 (Feb) 1947. (c) Lewis, G M, and Cormia, F E. Eosinophilic Granuloma. Theoretical and Practical Considerations Based on the Study of a Case, *ibid* 55 176 (Feb) 1947. (d) Lever, W F. Eosinophilic Granuloma of the Skin. Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone, Report of a Case, *ibid* 55 194 (Feb) 1947. (e) Curtis, A C, and Cawley, E P. Eosinophilic Granuloma of the Bone with Cutaneous Manifestations. Report of a Case, *ibid* 55 810 (June) 1947.



Fig 1 (case 1) —Four sharply demarcated purplish, slightly elevated plaques are present.



Fig 2 (case 1) —Low magnification. The upper part of the corium is occupied by a diffuse infiltrate. A greatly dilated vessel is present in the center ($\times 100$)



Fig 3 (case 1)—High magnification. The infiltrate is composed largely of eosinophils and polymorphonuclear leukocytes. The remaining cells are almost all histocytes. The greatly dilated capillary shows swelling of its endothelium ($\times 400$)

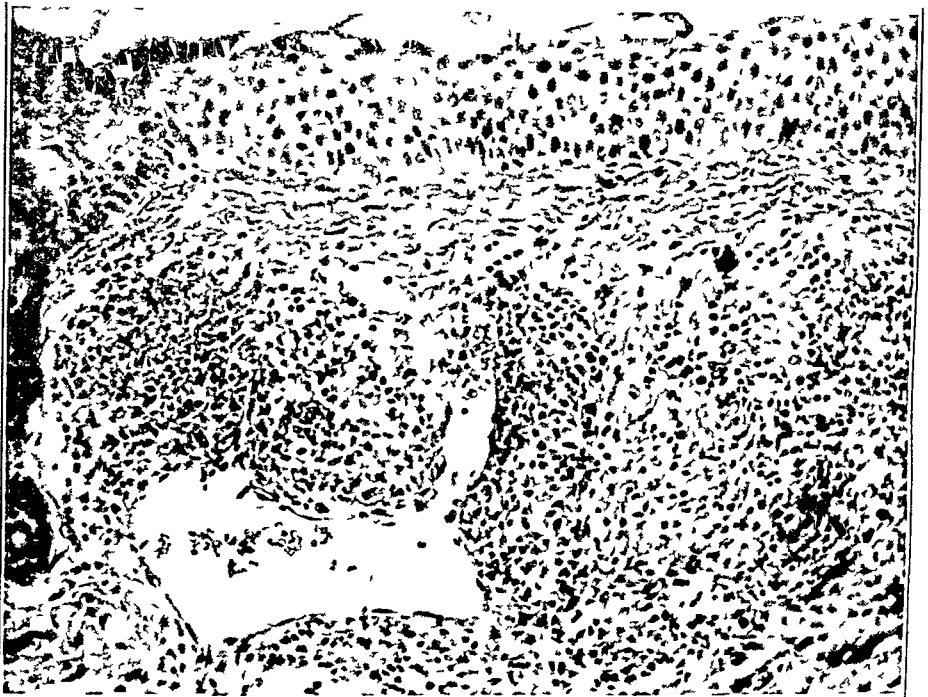


Fig 4 (case 2)—An area taken from the border of the lesion shows the earliest stage. The infiltrate is not yet diffuse but is perivascular. The collagen is edematous. A greatly dilated capillary is shown. At the left upper pole of this capillary a focus of hemorrhage is present ($\times 200$)

almost elastic to the touch. It was slightly irregular and felt nodular in parts. The lesions showed the following distribution (fig 1) one in the left preauricular region, measuring 2.7 by 3.6 cm, one in the left zygomatic region, measuring 2.9 by 3.1 cm, one in the left infraorbital region, measuring 2.2 by 1.3 cm, and one just inferior to this last lesion, measuring 0.4 by 0.6 cm. General physical examination, as well as roentgenologic examination of the skull and long bones revealed no abnormalities.

A biopsy revealed that the epidermis was of normal thickness, but the rete pegs were absent in most areas. Except for a narrow band of normal collagen directly beneath the epidermis, the upper half of the corium was occupied by a diffuse infiltrate (fig 2). The infiltrate was densest around the capillaries. In the lower half of the corium, the infiltrate, instead of being diffuse, consisted of variously sized irregular patches. In a few areas it extended into the subcutaneous fat. The infiltrate was composed largely of eosinophils and polymorphonuclear leukocytes (fig 3). In some areas these two types of cells constituted as much as 80 per cent of the infiltrate. The eosinophils were in part mononuclear and in part polymorphonuclear. The cytoplasm of the eosinophils only rarely showed distinct eosinophilic granules, usually it stained homogeneously eosinophilic. Frequently it was difficult to decide whether a given cell was an eosinophil or a neutrophil. The remaining cells of the infiltrate were almost all histiocytes. In only a few areas were a few lymphocytes and plasma cells noted. No areas of necrosis or abscess formation were seen. There were small foci of extravasated erythrocytes. Considerable amounts of hemosiderin were present throughout the infiltrate, but particularly in its upper portion. The hemosiderin was found extracellularly as well as within histiocytes. The capillaries were dilated, some of them considerably. They showed swelling of the endothelium. An occasional blood vessel showed fibrosis of its wall. The cutaneous appendages were normal, they were not invaded or destroyed by the infiltrate.

Staining for reticulum fibers (Foot stain) revealed a delicate densely meshed network of reticulum fibers throughout the infiltrate surrounding in some areas individual cells, but in most areas small groups of cells. An iron stain revealed that all the pigment present in the infiltrate was hemosiderin.

CASE 2—A 40 year old man noted an asymptomatic purplish patch in the left preauricular region in April 1946. In January 1947 two small lesions appeared close to the original one. Examination on January 25 revealed a sharply demarcated, purplish red, slightly raised, soft irregularly infiltrated plaque in the left preauricular region, measuring 2 by 4 cm in diameter, and two similar lesions, 0.3 cm in size, close to the large lesion. A biopsy was done at that time. In August the large lesion had increased in size and had become confluent with the two satellite lesions. The entire area now measured 2.2 by 5 cm. The lesion was excised and the defect closed with a full thickness skin graft.

The biopsy specimen of January 25 was obtained from the periphery of the lesion. It showed essentially the same histologic appearance as that in case 1. There was a conspicuous amount of extravasated red blood cells. At the border of the lesion the infiltrate was not diffuse, but clearly perivascular. The collagen showed edema. Even at this earliest stage the vessels showed dilatation, and foci of hemorrhages were present (fig 4).

The specimen obtained at the time of complete excision showed a variable picture. At the margin the infiltrate was essentially the same as that observed

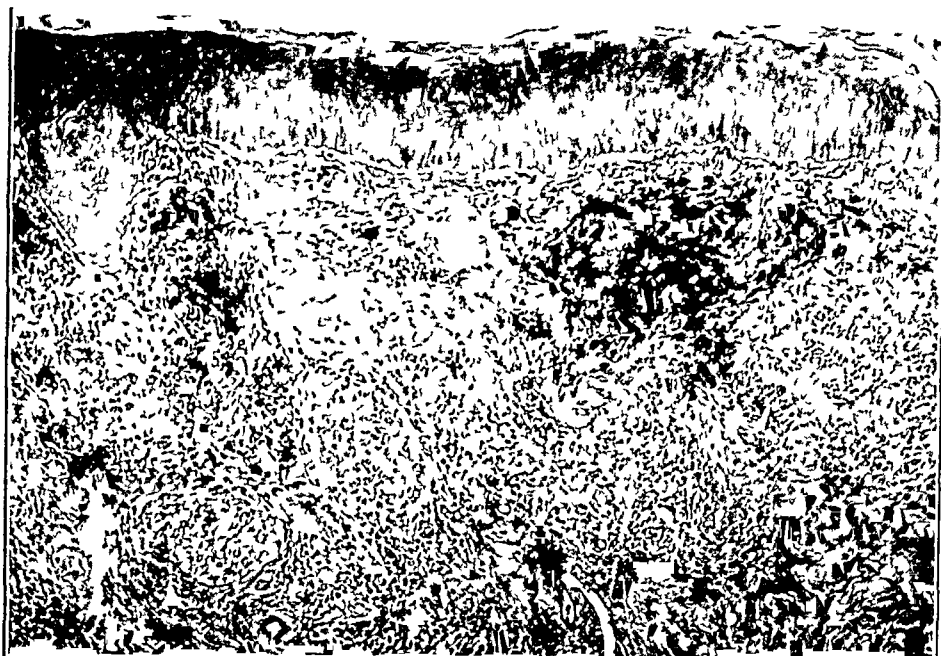


Fig 5 (case 2) —Potassium ferrocyanide stain for iron The infiltrate shows beginning fibrosis Deposits of hemosiderin are present throughout the infiltrate, particularly in the upper part of the corium ($\times 100$)

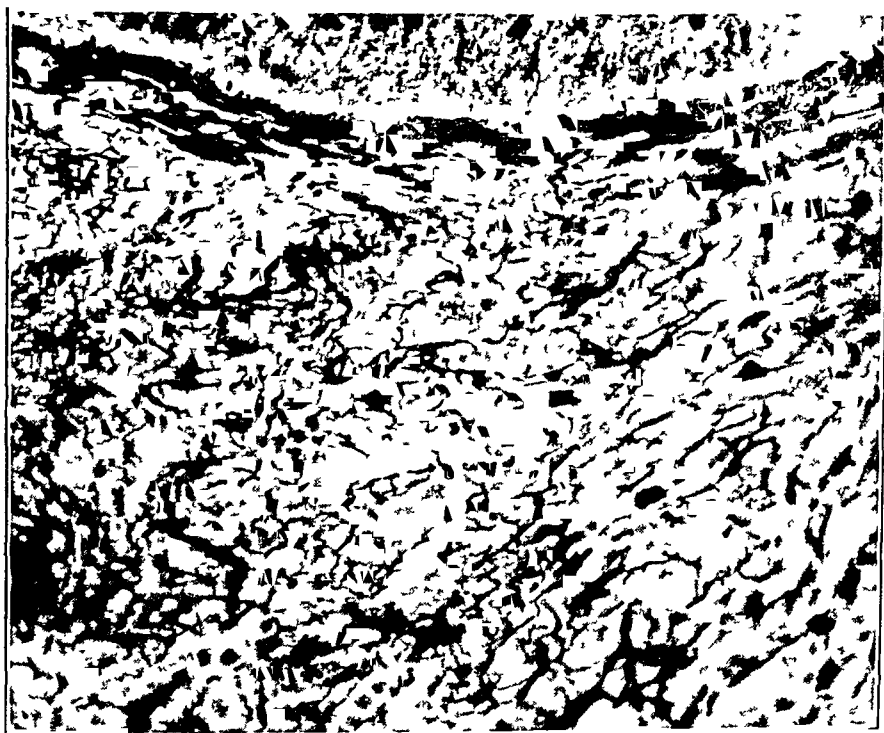


Fig 6 (case 2) —Reticulum stain (Foot) On the left, where the infiltrate is composed predominantly of eosinophils and leukocytes, the reticulum network is finely meshed and the fibers themselves are delicate On the right, where there is beginning fibrosis, the reticulum fibers are fewer and thicker ($\times 400$)

in case 1 In the center the infiltrate was diffuse in some areas, while in others it was traversed by bands of collagen The composition of the infiltrate varied In areas of diffuse infiltration eosinophils and neutrophils were in the majority In areas of beginning fibrosis, histiocytes, fibroblasts, lymphocytes and plasma cells were more numerous than eosinophils and neutrophils The lymphocytes and plasma cells had a tendency to lie in focal collections In areas of beginning fibrosis extravasation of erythrocytes was scarce or absent The amount of hemosiderin, however, was considerable (fig 5) The blood vessels located in areas of fibrosis showed fibrotic thickening of their walls

Staining for reticulum fibers (Foot stain) showed a reticulum network of varying denseness (fig 6) In areas in which eosinophils and neutrophils predominated, the reticulum network was finely meshed and the fibers themselves delicate In areas undergoing fibrosis, the reticulum fibers were fewer and thicker One could easily observe in many areas the transformation of reticulum fibers into collagen fibers

Chemical analysis of the excised lesion revealed the values shown in table 1 (Dr S J Thannhauser performed these tests)

CASE 3—A 53 year old man was first seen on March 14, 1947, with the complaint of an asymptomatic slowly growing lesion in the right temple area, of six months' duration The lesion measured 0.8 cm in diameter, was reddish

TABLE 1—Results of Chemical Analysis of Lesion in Case 2

	Sample with Lesion, Mg /100 Mg	Sample Without Lesion, Mg /100 Mg
Cholesterol (total)	0.230	0.342
(free)	0	0
Phospholipids (total)	1.490	1.280

purple, sharply demarcated, slightly elevated and soft and elastic to the touch The lesion was excised Examination on July 11 revealed that there was no recurrence at the site of excision However, when on this date the patient was given a general examination, four lesions were noted on the back The patient had not been aware of their presence The largest lesion was located at the medial border of the left scapula and measured 1.1 by 0.7 cm (fig 7) Two lesions measuring 4 mm each were present on the right shoulder, and one measuring 3 mm was present over the left scapula A biopsy of the largest lesion was performed

The two excised lesions, one from the face and one from the back, showed essentially the same histologic picture In a few areas, the infiltrate was diffuse and composed predominantly of eosinophils and polymorphonuclear neutrophils In most areas, however, the infiltrate was divided into irregular patches by fibrotic collagen, and was composed predominantly of histiocytes, fibroblasts, lymphocytes and plasma cells, with only a few eosinophils and neutrophils Small amounts of hemosiderin were present in the upper part of the corium Fibrosis of the walls of vessels was a prominent feature (fig 8)

COMMENT

The clinical and histologic appearance in the 19 cases of eosinophilic granuloma so far described in the literature is not uniform, except that the histologic picture in all cases is characterized by numerous

eosinophils and histiocytes. However, in the cases reported by Pasini² Wigley,³ Buley^{1a} and Lever^{1d} and in the 3 presently reported there was such uniformity in the clinical and histologic appearance that the condition may well represent an entity apart from that in the other cases described under the diagnosis of eosinophilic granuloma of the skin. Taking Weidman's classification^{1b} as a basis, they all represent the symptomatic type of eosinophilic granuloma of the skin. This type may be related to erythema elevatum diutinum.

On clinical examination, the lesions in the 7 patients consisted of sharply demarcated, slightly raised purplish plaques covered by a normal epidermis. They had a soft, almost elastic consistency. In the larger lesions a few nodular irregularities could be felt. The lesions were asymptomatic. They showed a tendency to increase slowly in size. Their number ranged from three to five. In 6 cases they were located

TABLE 2—*Clinical Features in 7 Patients with Eosinophilic Granuloma of the Skin*

	Age of Patient	Sex	Duration (Yr.)	Number of Lesions	Location of Lesions	Size of Largest Lesion
Pasini ²	69	F	8	4	Face	10.0 cm (?)
Wigley ³	46	F	2	4	Face	1.0 cm
Buley ^{1a}	49	M	16	3	Face	0.8 cm
Lever ^{1d}	47	F	11	3	Face	5.5 cm
Case 1	52	M	4	4	Face	3.6 cm
Case 2	40	M	1½	3	Face	5.0 cm
Case 3	53	M	½	5	Face and back	1.1 cm

exclusively on the face. In 1 case there were, in addition to one lesion on the face, four lesions on the upper part of the back (table 2).

On histologic examination an early (leukocytic) and a late (fibrotic) stage could be recognized. In several cases the two stages were present simultaneously. In Wigley's³ and Buley's^{1a} cases and in case 1, the lesions were those of the early stage. In Pasini's² case and case 2, beginning fibrosis was apparent. In Lever's^{1d} case and case 3, there were, in addition to areas in the early stage, areas of pronounced fibrosis. Lesions in the early stage showed a diffuse infiltrate which was densest about the capillaries. It was composed of eosinophils, neutrophils and histiocytes. The eosinophils were predominantly polymorphonuclear, but some were mononuclear. The capillaries were decidedly dilated and showed swelling of the endothelial cells. In some cases there were areas of extravasation of red cells and deposits of hemosiderin (Lever's case^{1d} and cases 1, 2 and 3). A dense net-

2 Pasini, A. Granuloma eosinofilo (reticulo-endoteliosi proliferativa), *Gior ital di dermat e sif* **81** 1, 1940.

3 Wigley, J. E. M. Sarcoid of Boeck, ? Eosinophilic Granuloma, *Brit J Dermat* **57** 68, 1945.

work of fine reticulum fibers permeated the infiltrate. The cutaneous appendages were preserved. Lesions in the late stage showed greater polymorphism of cell types. The number of eosinophils and neutro-

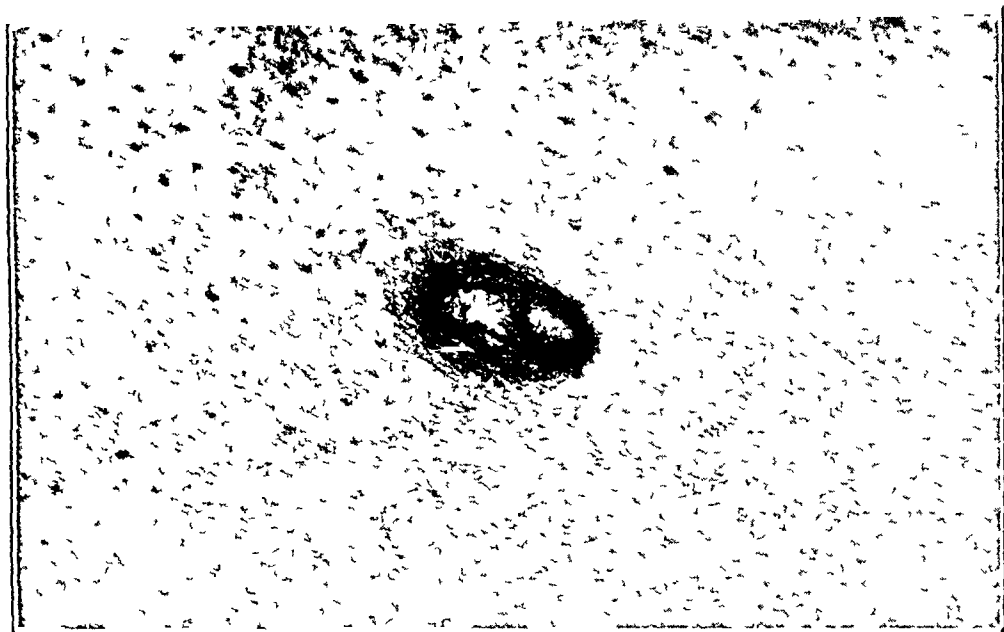


Fig 7 (case 3) —The largest of the four lesions on the back is shown

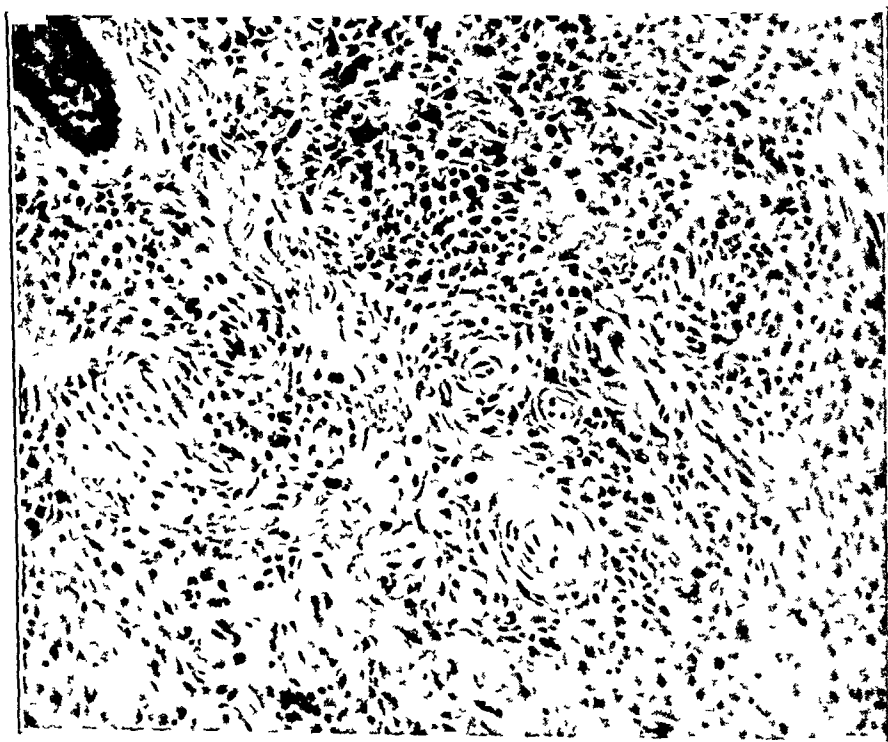


Fig 8 (case 3) —The infiltrate shows a considerable degree of fibrosis. The infiltrate is composed predominantly of histiocytes, fibroblasts, lymphocytes and plasma cells. Only a few eosinophils and leukocytes are present. The vessels show thickening and fibrosis of their walls ($\times 200$)

phils was greatly decreased, and lymphocytes, plasma cells and fibroblasts were present. The infiltrate, instead of being diffuse, was broken

up into irregular patches by thick strands of collagen. The walls of the vessels showed thickening and fibrosis of their walls. On staining for reticulum the transformation of reticulum fibers into collagen fibers could be observed in many areas. Foam cells and stainable lipids were found in only 1 of the 7 cases^{1d}. Phagocytic activity was evident, however, in several other cases (cases 1, 2 and 3), inasmuch as hemosiderin was present within histiocytes.

It is not possible at the present time to decide whether or not eosinophilic granuloma of the skin is related to eosinophilic granuloma of the bone. So far, no unquestionable case with lesions of the bone as well as of the skin has been described. In Curtis and Cawley's case^{1e} of eosinophilic granuloma of the bone with cutaneous manifestations, the lesions may have been those of Letterer-Siwe disease. In that disease, cutaneous as well as osseous lesions are known to occur.

Apparently eosinophilic granuloma of the skin is not a rare disease. It can, therefore, be expected that additional cases will soon accumulate, permitting a more exact appraisal of the nosologic position of this disease.

SUMMARY

Three cases of eosinophilic granuloma of the skin are added to the 19 cases recorded in the literature. In the 19 cases so far reported there was no uniform clinical and histologic appearance, except that histologic examination in all revealed numerous eosinophils and histiocytes.

However, in 4 of the reported cases and in the 3 presently reported there was such uniformity in clinical and histologic appearance that the disease in these cases may well represent an entity apart from that in the other cases.

ORAL IODINE THERAPY IN ACNE VULGARIS

Failure of Iodine, or the Equivalent of Iodized Salt, to Produce
Pustular Exacerbations

L EDWARD GAUL, M D

AND

G B UNDERWOOD, M D

EVANSVILLE, IND

EARLY in 1945, various iron salts were being screened in patients with acne. The purpose was to study the effects of either the cation or the anions. An iron deficiency is common among adolescent girls. M B was a white married woman, aged 22, with pustular acne of six years' duration. In addition to routine therapy, she received ferrous iodide. An excellent clinical result attended the supplement. A sister, D C, aged 19, presented a similar eruption, of four years' duration. Identical treatment was instituted with the exception that ferrous sulfide was prescribed. Her result was poor. Other patients with acne had received ferrous sulfide with indifferent effects. The subsequent course of the acne in these sisters made us consider that iodine may have influenced their response to treatment.

Cautiously iodine was prescribed for other patients. Two patients (cases 38 and 41) received an average of 56 mg weekly (table). During twelve and ten weeks, respectively, of critical inspection, no exacerbations were noted. The improvement in their acne was ahead of schedule. The dosage in succeeding cases was then slightly increased. Weekly inspections failed to reveal any exacerbation. Thirty-four cases were observed over varying periods of time after iodine therapy was stopped. No late exacerbations were apparent. The amount of iodized salt required to supply an equivalent of iodine suggests that on a quantitative basis iodized salt does not unfavorably affect the course of acne vulgaris.

CLINICAL OBSERVATIONS ON IODINE SUPPLEMENT IN ACNE

A study of a possible iodine deficiency in acne has been under way over three years. Encouraging results have been obtained. The supplemental dosage has averaged about 280 mg per week. The following clinical effects have been noted: 1 A flushing of the acne areas during the first month. This is especially apparent in patients with a sallow or yellowish complexion. 2 A gain in weight in the tall and slender persons. 3 The disappearance of comedos after three to six

*Oral Iodine Dosage Compared with Intake from Iodized Salt **

Case No	Patient	Age, Yr	Sex	Iodine Compound	Weekly Iodine Dosage, Mg	Weeks of Therapy	Total Iodine Intake, Gm	Inspection During Iodized Salt Therapy, Weeks	
								Iodine lent per Ther Weeks	Equivalent of Therapy, Kg †
1	J A	20	F	Strong iodine solution†	0 336	14	4 7	19	62
2	S A	17	M	Strong iodine solution	0 168	9	1 51	9	20
3	H A	16	I	Strong iodine solution	0 112	19	2 12	19	28
4	M B	15	I	Strong iodine solution	0 560	8	4 48	8	59
5	A B	32	F	Strong iodine solution	0 168	15	2 52	15	33
6	D B	15	M	Potassium iodide	0 700	8	5 6	11	74
7	J B	14	M	Strong iodine solution	0 112	8	0 89	16	11
8	L B	19	F	Strong iodine solution	0 560	17	9 5	17	126
9	C B	18	M	Strong iodine solution	0 224	8	1 79	19	23
10	J B	14	F	Strong iodine solution	0 280	8	2 24	8	29
11	P B	15	F	Strong iodine solution	0 280	4	1 12	4	15
12	M B	17	F	Strong iodine solution	0 448	9	4 03	9	53
13	J B	17	F	Strong iodine solution	0 280	16	4 48	16	59
14	M B	22	F	Ferrous iodide	1 45	15	21 75	39	290
15	D C	19	F	Strong iodine solution	0 112	14	1 56	14	20
16	E C	13	F	Strong iodine solution	0 168	17	2 85	17	38
17	B C	23	F	Strong iodine solution	0 336	10	3 36	25	44
18	E C	21	M	Strong iodine solution	0 336	15	5 04	21	67
19	F C	22	F	Strong iodine solution	0 560	10	5 60	13	74
20	M C	19	F	Strong iodine solution	0 280	9	2 52	14	33
21	V D	17	I	Strong iodine solution	0 560	4	2 24	4	29
22	J D	21	M	Strong iodine solution	0 224	20	4 48	21	59
23	E D	14	M	Strong iodine solution	0 112	19	2 12	31	26
24	N E	22	F	Strong iodine solution	0 280	13	3 64	13	48
25	J E	14	F	Strong iodine solution	0 280	22	6 16	25	82
26	P E	18	F	Ferrous iodide	1 45	8	11 6	17	154
27	G F	15	M	Strong iodine solution	0 168	24	4 03	24	53
28	J F	21	F	Strong iodine solution	0 280	7	1 96	7	26
29	M F	17	F	Strong iodine solution	0 560	17	9 52	23	126
30	V G	17	I	Strong iodine solution	0 168	19	3 19	29	42
31	B G	18	F	Strong iodine solution	0 112	8	0 89	16	11
32	G G	21	M	Strong iodine solution	0 280	7	1 96	10	26
33	J H	13	M	Strong iodine solution	0 168	7	1 17	7	15
34	M H	17	F	Strong iodine solution	0 280	8	2 24	9	29
35	S H	18	M	Strong iodine solution	0 280	11	3 08	11	41
36	B H	21	F	Strong iodine solution	0 168	14	2 30	18	30
37	M H	18	F	Strong iodine solution	0 280	8	2 24	8	29
38	M J	20	F	Strong iodine solution	0 056	12	0 67	12	8
29	J J	16	F	Strong iodine solution	0 112	5	0 56	12	7
40	V K	14	F	Strong iodine solution	0 168	5	0 84	7	11
41	A L	18	F	Strong iodine solution	0 056	8	0 44	10	5
42	D L	23	I	Strong iodine solution	0 280	10	2 80	10	3
43	P L	13	F	Strong iodine solution	0 280	13	3 64	13	48
44	J L	13	M	Strong iodine solution	0 168	10	1 68	17	22
45	V M	23	F	Strong iodine solution	0 280	13	3 64	13	48
46	A M	17	F	Ferrous iodide	1 45	14	20 30	16	270
47	P M	17	F	Strong iodine solution	0 280	15	4 20	19	56
48	C N	29	F	Strong iodine solution	0 280	16	4 48	16	59
49	R P	16	M	Strong iodine solution	0 224	10	2 24	10	29

Oral Iodine Dosage Compared with Intake from Iodized Salt*—Continued

Case No	Patient	Age, Yr	Sex	Iodine Compound	Weekly Iodine Dosage, Mg	Weeks of Therapy	Total Iodine Intake, Gm	Inspection During Iodized Salt After Equiva Iodine lent per Ther- Weeks of Therapy, Weeks	Kg †
50	W P	15	M	Strong iodine solution	0.250	20	5.60	45	74
51	E P	20	F	Potassium iodide	0.700	10	7.00	12	93
52	G R	21	M	Strong iodine solution	0.036	8	0.448	18	5
53	J R	16	F	Strong iodine solution	0.250	9	2.52	9	33
54	A B.	17	F	Strong iodine solution	0.224	20	4.48	25	59
55	E R	17	F	Strong iodine solution	0.165	8	1.32	8	17
56	E S	14	F	Strong iodine solution	0.280	6	1.68	6	22
57	E S	27	M	Strong iodine solution	0.112	7	0.78	7	10
58	O S	20	F	Strong iodine solution	0.165	5	0.84	5	11
59	C S	18	M	Strong iodine solution	0.250	7	1.96	7	26
60	J S	19	F	Strong iodine solution	0.250	10	2.80	14	37
61	M S	17	F	Strong iodine solution	0.280	13	3.64	13	48
62	I S	20	F	Strong iodine solution	0.280	9	2.52	9	33
63	S S	15	F	Strong iodine solution	0.165	7	1.17	7	75
64	O S	26	M	Strong iodine solution	0.224	12	2.68	15	35
65	M U	13	F	Strong iodine solution	0.165	4	0.67	4	8
66	R W	17	F	Potassium iodide	0.700	9	6.30	9	8
67	J W	15	M	Strong iodine solution	0.280	18	5.04	22	67
68	W W	20	M	Strong iodine solution	0.165	23	3.86	23	51
69	P W	16	M	Strong iodine solution	0.250	7	1.96	7	26
70	R W	19	F	Strong iodine solution	0.280	8	2.24	8	29
71	P W	17	F	Strong iodine solution	0.280	11	3.08	11	41
72	C W	20	F	Potassium iodide	0.700	12	8.4	40	112
73	H W	20	F	Strong iodine solution	0.280	8	2.52	9	33
74	F W	27	M	Strong iodine solution	0.280	11	3.08	11	41
75	R W	17	M	Strong iodine solution	0.280	10	2.80	10	38
76	M W	24	F	Potassium iodide	0.700	11	7.70	11	102
77	U Y	14	M	Strong iodine solution	0.280	16	4.48	21	59
78	N C	25	F	Strong iodine solution	0.280	16	4.48	16	59
79	L B	38	F	Strong iodine solution	0.224	4	0.89	4	11

* If the potassium iodide in iodized salt is not properly stabilized, the iodine content will rapidly migrate out of the product. The migration is favored by unusual conditions of temperature, humidity, sunlight, duration of storage and particularly the presence in the salt of inorganic salts of iron, copper and manganese. The use of iodized salt does not assure a uniform monthly intake of iodine. The iodine content may vary from the accepted level, 0.01 per cent to essentially 0. (From the Morton Salt Co. and Michigan and New York state departments of health.)

† Household salt is usually marketed in 26 ounce (454 Gm.) paper cartons.
1 mgol = solution

weeks 4 The lesions in colloid and cystic acne apparently undergoing liquefaction with the spontaneous drainage 5 A clearing and brightening of the complexion 6 A smoothening of the skin 7 A favorable effect on the sequela pits and scars

REPORT OF A CASE

J E, a white girl, aged 14, was seen early in May 1947 for severe acne of two years' duration. Comedones and pustules dotted the forehead, sides of the face, chin and neck. Lesions were present in all stages of evolution and involution. Deep pits showed the sites of healed lesions. The cheek prominences were occupied by a mass of hazelnut-sized purplish cysts.

The usual acne regimen was advised and roentgen therapy, 75 kilovolts, 5 milliamperes, 25 cm, 1 minute (80 r), each week. Twelve weeks of treatment produced no improvement. A consultation was obtained and the recommendations carried out. Four weeks of additional therapy had no effect. The cysts continued to deform the cheeks, comedones kept appearing and resolving as pustules. On September 12, iodine therapy was started, 5 drops daily of strong iodine solution. A week later, this was reduced to 3 drops daily. By October 10, all the active lesions had involuted. The iodine supplement was continued until December. She was discharged at this time with an excellent result.

DEVELOPMENTAL, ENVIRONMENTAL AND BIOCHEMICAL EVIDENCE OF A POSSIBLE IODINE DEFICIENCY IN ACNE

Four phases of growth are distinguished from birth to adulthood. The first phase of growth is rapid. It decelerates about the end of the second year. From the second to the tenth or eleventh year, the growth is about uniform, a weight gain of 2 to 2.8 Kg per year. The third phase is characterized by a "spurt" in weight and height, associated with sexual maturity and puberty.¹ Acne eruptions usually appear during or after this rapid phase of development. If iodine requirements are minimal or subminimal during the prepuberty years, sudden growth would tend to produce a severe deficiency. The dietary histories of patients with acne have commonly revealed that the bulk of their calories came from food low or deficient in iodine. As the growth curve flattens out, an iodine deficiency would gradually be overcome. After varying periods following puberty, acne lesions tend to disappear.

During the fall of 1947 over 500 male high school freshmen and sophomores were given the "line type" dermatologic examination. These boys were going through or had just completed their most rapid development. To observe the acne areas free from comedones or pustules was rare. The examinations were made toward the close of two months of extremely hot and humid weather. The sweat glands are accessory organs for the loss of iodine from the body. An important nutritional question with reference to iodine metabolism is the effect of a hot environment on the losses of iodine from the body and on iodine requirements, particularly as this effect may involve the activity of the

¹ Nelson, W. E. Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945.

sweat glands² Of interest in this respect are the reports³ on tropical acne

About 10 per cent of the body iodine is present in the skin Increased excretion of iodine in the urine has been observed during menstruation, pregnancy, acute infections and during periods of excitement⁴ The thyroid is apparently the site for the conversion of dietary carotene into vitamin A⁵ Iodine is an essential component of the thyroid hormone If a dietary lack of iodine affects the ability of the thyroid to form vitamin A, it is possible that a cutaneous deficiency of this vitamin may be in part an iodine deficiency The observation of keratotic plugging of the sweat ducts in prickly heat⁶ may be proved to reflect a deficiency of one or both of the components necessary for the thyroid to elaborate vitamin A Future investigations may well revise upward the dietary requirements of iodine

CONCLUSION

The total iodine intake and the weeks of observations during and after iodine therapy suggest that, on the basis of the cases herein discussed, iodized salt does not unfavorably affect the course of acne vulgaris

2 Spector, H , Mitchell, H H , and Hamilton, F S The Effect of Environmental Temperature and Potassium Iodide Supplementation on the Excretion of Iodine by Normal Human Subjects, *J Biol Chem* **161** 137, 1945

3 Novy, F G , Jr Tropical Acne, *California Med* **65** 274, 1946 Allington, H V Acne Vulgaris Occurring in the Tropics in a Pigmentary and Pilosebaceous Nevus, *Arch Dermat & Syph* **52** 322 (Nov-Dec) 1945 Sulzberger, M B Tropical Acne, in *Year Book of Dermatology and Syphilology, 1944-1945*, Chicago, The Year Book Publishers, Inc , 1946, p 281

4 Cantarow, A , and Trumper, M Clinical Biochemistry, ed 3, Philadelphia, W B Saunders Company, 1945, p 215

5 The Thyroid and Vitamin A, editorial, *J A M A* **137** 91 (May 1) 1948

6 Sulzberger, M B , and Zimmerman, H M Studies on Prickly Heat, *J Invest Dermat* **7**:61, 1946

GUMMA OF THE LUNG

Report of a Case

DAVID F. BRADLEY, M.D.

NEW ORLEANS

GUMMA of the lung is conceded by most writers on the subject to be a rarity, especially as a manifestation of acquired syphilis. The diagnosis of gumma of the pulmonary parenchymal tissue in all cases heretofore reported has been either clinical or established at necropsy. The case to be reported is unique in that the disease was suspected clinically and confirmed histologically in a living patient by examination of lung tissue removed by lobectomy.

It is not within the scope of this report to review the literature, as little has been added since the presentation of Carrera¹ in 1920.

The diagnosis of gumma of the lung rests on several criteria, which may be divided into four broad categories: clinical, radiologic, therapeutic and pathologic.

Clinically, there is little to distinguish gumma of the lung from a host of other localized chronic pulmonary lesions, particularly tuberculosis, deep mycoses of the actinomyces and nocardia groups, discrete areas of pneumonitis of bacterial origin, neoplasms, localized bronchiectasis and pulmonary abscess. The criteria outlined by Pearson and De Navasquez,² as quoted by Kulchar and Windholz,³ seem adequate.

1 An anomalous history of pulmonary disease, often with hemoptysis, productive cough, loss of weight, and fever, either of brief duration or extending over a period of years.

2 Exclusion of the commoner causes of pulmonary symptoms such as pneumonia, neoplasm, fungous infections, and tuberculosis, the latter by repeated failure to find tubercle bacilli in the sputum.

3 The presence of a history of syphilitic infection or associated syphilitic lesions in other organs and of a positive serologic test for syphilis.

4 The effect of antisyphilitic treatment on the lesion.

5 X-ray appearance, particularly in association with the response to treatment.

From the Department of Dermatology, College of Physicians and Surgeons, Columbia University and the Vanderbilt Clinic, New York.

1 Carrera, J. L. A Pathologic Study of the Lungs in One Hundred and Fifty-Two Autopsy Cases of Syphilis, *Am J Syph* **4** 1, 1920.

2 Pearson, R., and De Navasquez, S. Syphilis of the Lung, *Guy's Hosp Rep* **88** 1, 1938.

3 Kulchar, G. V., and Windholz, F. The Clinical, Radiologic and Pathologic Aspects of Late Pulmonary Syphilis. Effects of Penicillin Therapy, *Am J Syph, Gonorr & Ven Dis* **31** 166, 1947.

As these criteria were postulated in 1938, prior to the era of penicillin therapy, some additions and revisions are in order. The drugs then in use, the arsenicals and heavy metals, could be considered relatively specific for lesions of syphilis, and the therapeutic test was a not absolute, but a highly suggestive, point in differential diagnosis. With the wide spectral range of penicillin among micro-organisms, a therapeutic test with this antibiotic can no longer be regarded as valid, especially in attempts to rule out pulmonary diseases in the nontuberculous bacterial group. It is well to remember, too, that a history of syphilis is often lacking and that tertiary lesions of syphilis have been known to occur in the absence of a positive serologic reaction. Another stumbling block frequently encountered is a false positive serologic reaction in the presence of pulmonary lesions of other than syphilitic origin. However, these are usually of low titer and of transient nature. Lesions of specific bacterial or mycotic origin can usually be ruled out by the isolation of the organism, either by direct examination or by cultural methods, and neoplastic lesions by their progression and lack of response to any type of therapy other than operation or irradiation.

It soon becomes obvious that the pitfalls to the absolute diagnosis of gumma of the lung are so numerous that only histologic examination of the diseased tissue will suffice. This conclusion is in agreement with that of Carrera after his exhaustive study of the subject. The diagnosis would be even more firmly established if *Treponema pallidum* could be found in the diseased tissue, in conjunction with the classic tissue reaction to syphilis. Only three investigators have found *T. pallidum* in the pulmonary lesions of acquired syphilis (Koch, Schmorl and Warthin). It is generally conceded, however, that this is not a *sine qua non*, provided that the tissue reaction is compatible with syphilis and that other diseases can be ruled out. In my case I did not find, nor did I expect to find, *T. pallidum* in the pathologic tissue, because large doses of penicillin had been administered prior to the removal of the gummatous lobe. Nevertheless, a careful but fruitless search for the organism was conducted by employment of the Levaditi staining technic. Acid-fast bacilli likewise could not be found.

REPORT OF A CASE

J. W., a 39 year old American Negro, applied for care at the Presbyterian Hospital on Oct. 27, 1947, with a chief complaint of "cough and cold in the left side of the chest" of thirty-seven days' duration. The patient stated that he had been well until September 20, when he had a slight chill, followed by the pain in the left side of the chest. The pain was dull and accentuated by his lying on his left side. Cough was productive of a small quantity of greenish yellow sputum. No rust-colored or bloody sputum was raised. He was seen by a local physician who had a pulmonary roentgenogram made, which the patient said showed a lesion

in the lower lobe of the left lung. He was given cough syrup, which relieved the cough slightly, but this recurred when the oral medication was discontinued. The pain also recurred, without change in intensity or location. There were no further chills, and he had never noticed night sweats. Since the onset of his illness, the patient had noticed moderate fatigue and dyspnea on exertion, and he had lost about 10 pounds (4.5 Kg) in weight.

There was no history of either primary or secondary lesions of syphilis. In 1927 the patient received two or three intravenous injections "for his blood." In 1945 a private physician gave him three injections in the hip, of an intended course of six, of "yellow medicine."

The patient had had a cystotomy in 1927 for "bladder stones," and at the same time the left testicle and the glans penis were removed. No further information about these measures could be obtained. Otherwise the past history was not

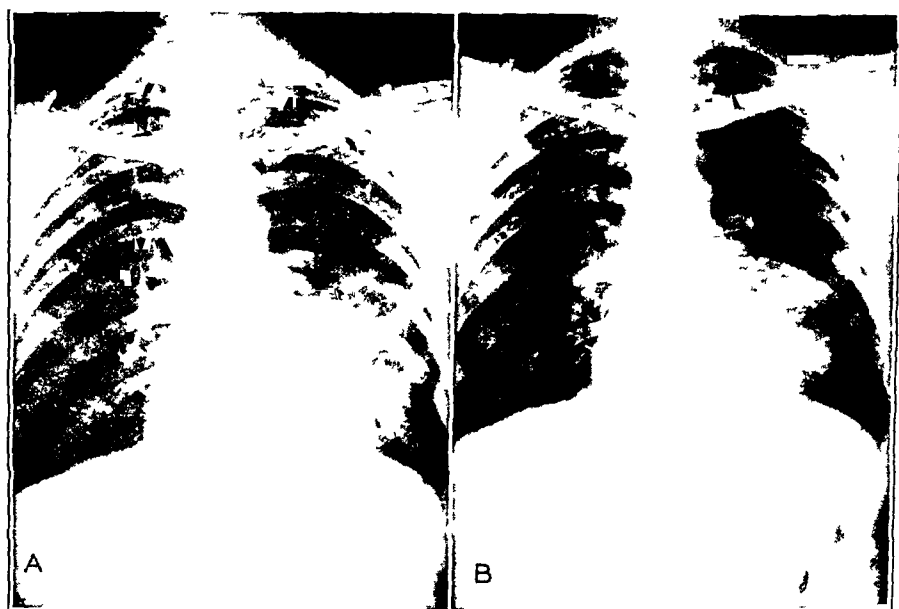


Fig 1—*A*, Roentgenogram of the chest, taken Oct 27, 1947, showing a localized inflammatory lesion in the lower lobe of the left lung. *B*, roentgenogram of November 26. After a month of penicillin therapy, the lesion shows only slight diminution in size.

remarkable, and the family history was noncontributory. No one in his immediate family had suffered from tuberculosis, to his knowledge.

On admission the patient's temperature was 98.4 F, pulse rate 75, respiration 18 and blood pressure 115 systolic and 80 diastolic. His general appearance was that of a well developed moderately emaciated Negro, who did not appear acutely ill. The pupils were round and equal and reacted to light and accommodation. There were no significant abnormalities of the nose, throat, neck or head. Examination of the heart revealed an organ of normal size without murmurs, thrills, arrhythmia or other remarkable signs. On percussion of the chest an area of dullness was noted over the lower lobe of the left lung posteriorly. Auscultation revealed tubular breathing with crepitant rales on inspiration over an area 5 cm in diameter below the inferior angle of the left scapula. On examination of the abdomen a scar in the suprapubic area was noted, but there were no other

abnormalities in this region. The glans penis and left testicle were absent. A stricture was noted on digital examination of the rectum. The prostate was normal in size and consistency. Deep and superficial reflexes were regarded as normal, as was appreciation of pain, temperature, touch, pressure and proprioception.

On the day of admission the hemoglobin was 13.4 Gm (Sahli), erythrocytes 4,400,000 and white blood cells 12,650, with a differential count of 62 polymorphonuclear leukocytes, 36 lymphocytes and 2 eosinophils. The erythrocytes revealed

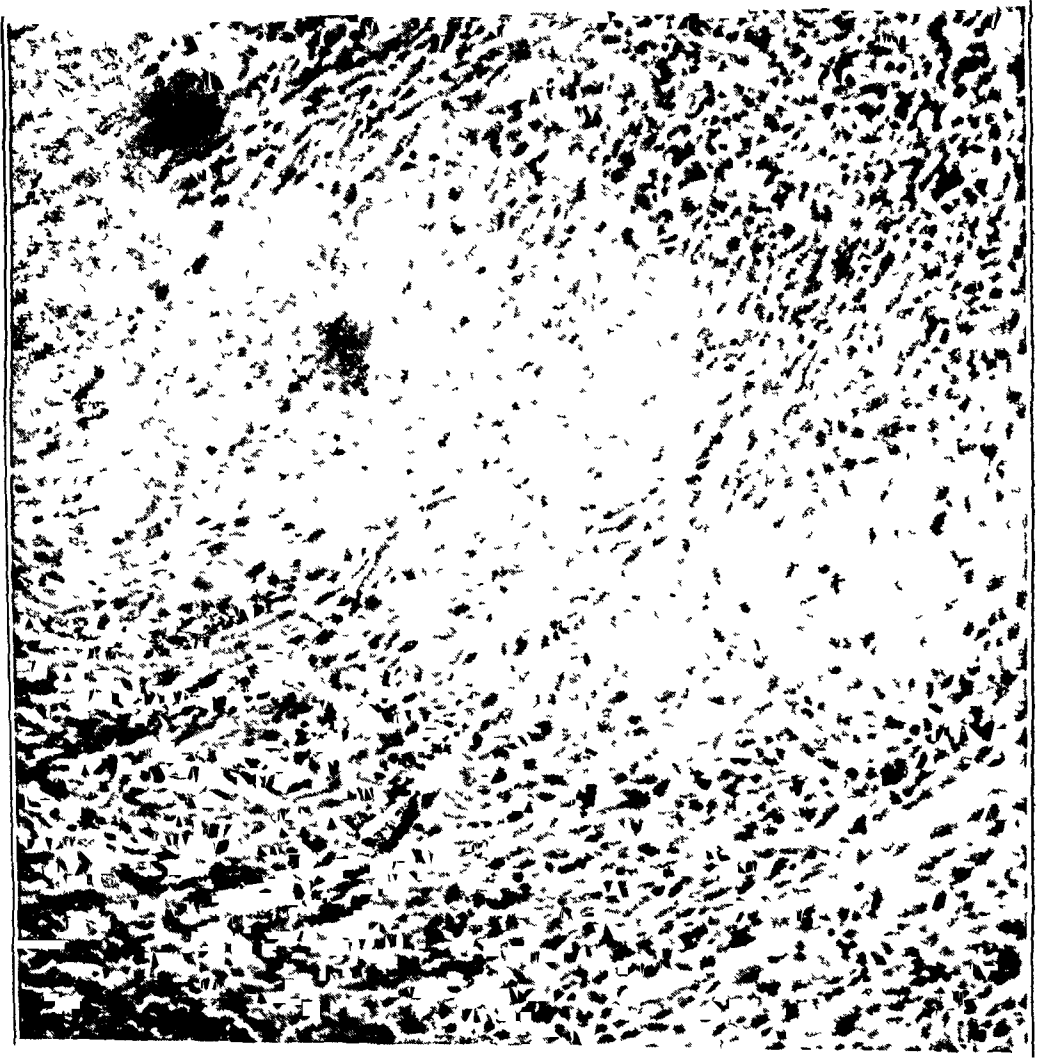


Fig 2—Low power photomicrograph showing caseation necrosis, and peripheral infiltration of plasma cells and lymphocytes

no anisocytosis or poikilocytosis, no malarial parasites were seen, and platelets were present in normal numbers. Succeeding hemograms were essentially the same.

Examination of the sputum revealed no acid-fast bacilli. Results of tests for cold agglutinins were negative.

A roentgenogram of the chest on October 27 (fig 1A) showed a large well defined lobulated shadow of increased density located posteriorly and medially in the left hemithorax. No abscess cavity was visualized.

On October 28 the erythrocyte sedimentation rate was 134 mm in sixty minutes.

Reexamination of the sputum on October 29 still revealed no acid-fast bacilli. A stool examination on the same date showed no ova or parasites. A thoracentesis was performed, but no fluid could be obtained. Serologic tests for syphilis on October 28 and October 30 gave strongly positive Kline and Wassermann reactions in both instances.

Acid-fast stains on October 31 again failed to reveal tubercle bacilli. Penicillin therapy was begun on this date, 400,000 units being given daily until November 12, when the dosage was increased to 1,000,000 units daily and continued through

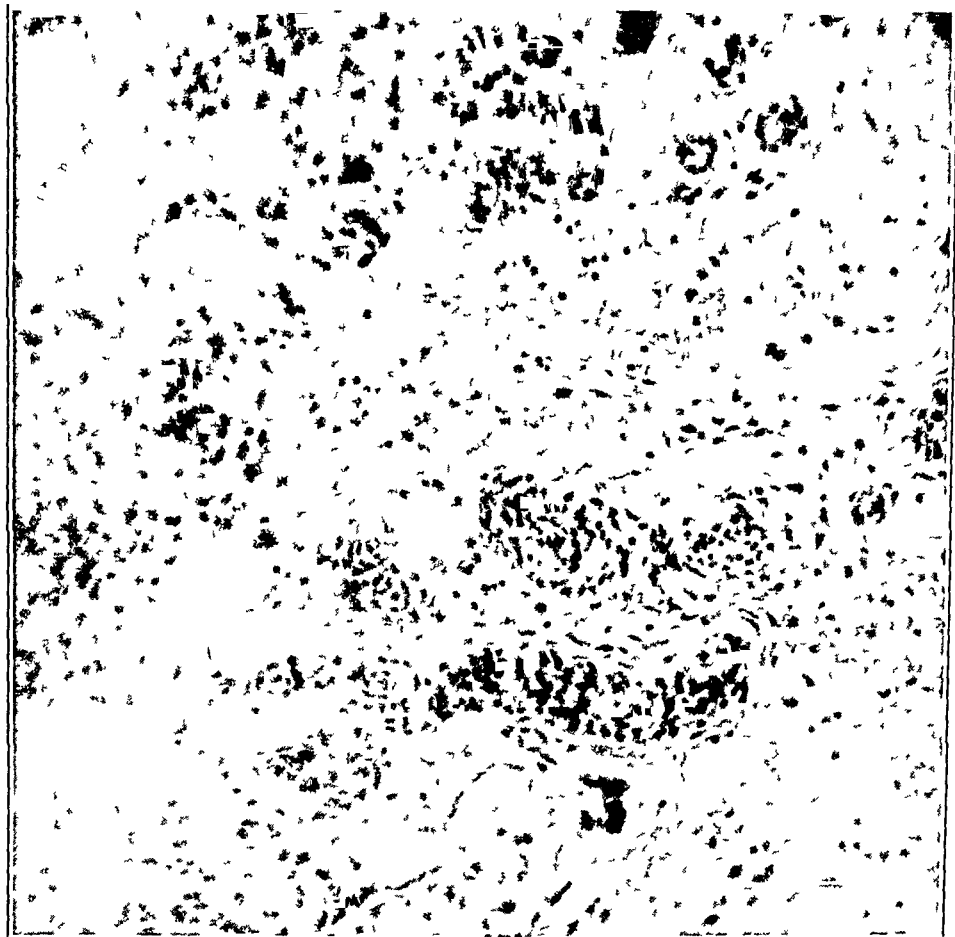


Fig 3—Low power photomicrograph of pulmonary tissue showing obliterative changes in small blood vessels and a sparse round cell infiltration. These elements have largely replaced the alveolar structure (hematoxylin and eosin).

November 27. The total quantity administered was 20,800,000 units. During this period, 200 mg of bismuth compound was given weekly and 45 drops of potassium iodide by mouth daily.

On November 3 lumbar puncture was performed and clear fluid obtained. Examination of this fluid showed 1 lymphocyte and 27 mg of protein. The Wassermann reaction and colloidal gold curves were negative.

Examination of the serum protein on November 5 showed a total of 9.1 Gm per hundred cubic centimeters, with albumin 4.3 Gm and globulin 4.8 Gm per hundred cubic centimeters.

Reexamination of the pulmonary lesion by roentgenogram on November 5 showed no appreciable change. Bronchoscopic examination on November 11 disclosed no abnormalities. Results of tuberculin tests were positive to a dilution of 1:100 and negative to 1:10,000.

By November 12 the patient was subjectively improved, although only slight improvement could be noted in the roentgenograms of the chest. The possibility of pulmonary neoplasm seemed real at this time, and a lobectomy was scheduled for December 2. Several roentgenograms during the intervening time still showed little change in the lesion (fig 1B). A lobectomy, of the lower lobe of the left

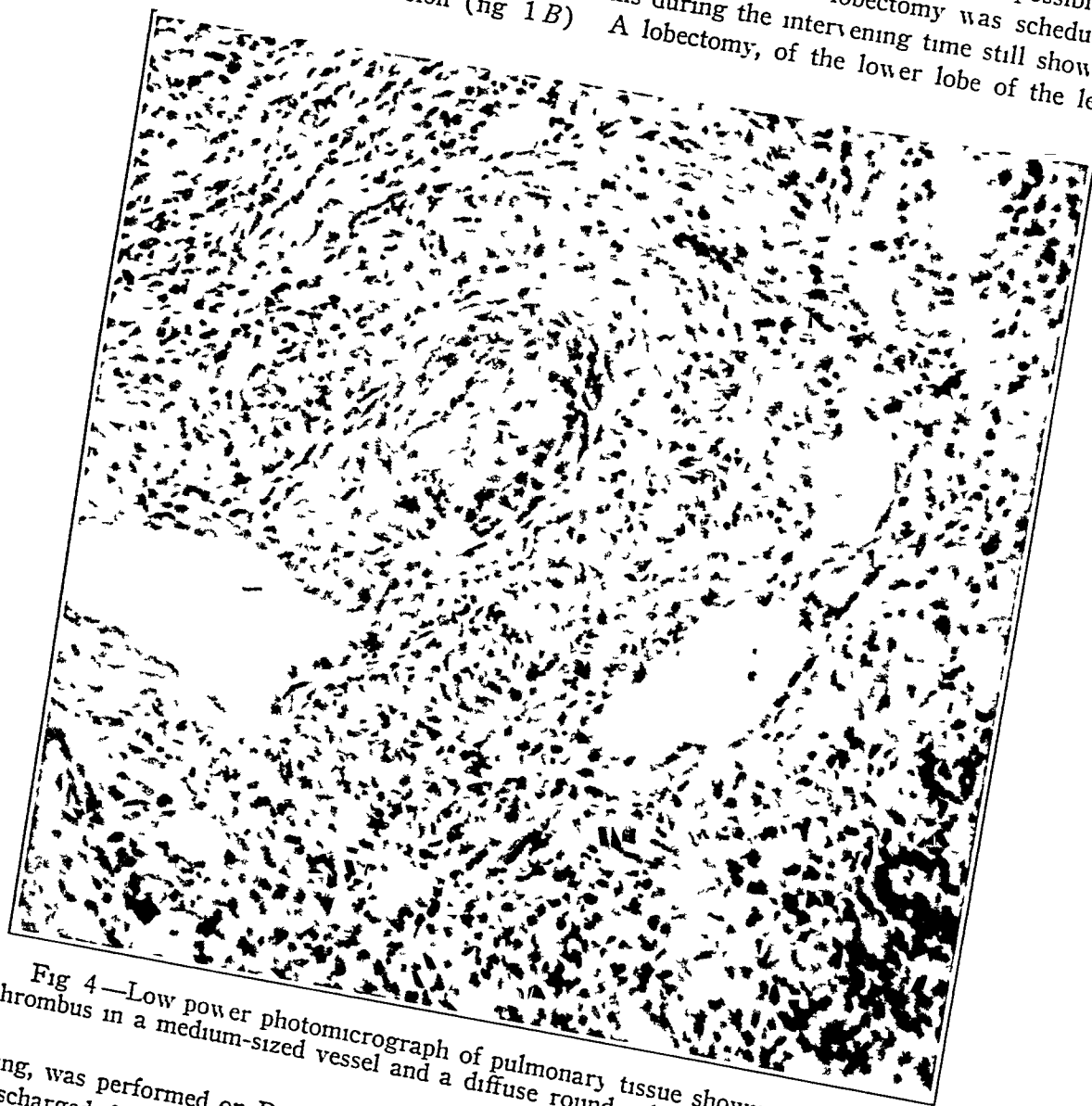


Fig 4—Low power photomicrograph of pulmonary tissue showing an organized thrombus in a medium-sized vessel and a diffuse round cell infiltrate.

lung, was performed on December 2, and the patient recovered uneventfully, being discharged from the hospital on December 12, to be followed in the outpatient department.

On three occasions since the patient's discharge from the hospital, serologic tests for syphilis were made, the last on June 3, 1948, and the Kline and Wassermann reactions of all specimens were strongly positive.

Gross pathologic examination of the tissue removed at operation revealed a firm irregular oval mass occupying the major portion of the lower lobe of the left

lung The visceral pleura was smooth and glistening, except for an area 7 by 5 cm. overlying the mass, where it was thickened, firm and light gray The cut surface revealed a wedge-shaped nodular mass 7 by 7 by 4 cm, situated at the periphery of the lung The mass was composed of firm gray well circumscribed nodules which extended to the pleura

Microscopic examination disclosed a multilocular lesion composed of necrotic fibrous tissue and lung parenchyma The normal lung architecture had been destroyed by enormous amounts of fibrous tissue which had in turn become necrotic (fig 2) The necrosis, however, for the most part, was of that type which leaves faint cellular and structural images It did not show the complete caseation necrosis typical of tuberculosis, nevertheless, there were a few areas where the necrosis was complete The fibrous tissue was cellular and not too dense in its arrangement An occasional multinucleated giant cell was seen

The remainder of the lung parenchyma also showed a disorganized arrangement of the alveoli due to widespread fibrosis The alveoli, when distinguishable, had swollen endothelial cells, giving the appearance of cuboidal epithelium Many alveoli had accumulations of large foamy macrophages In addition, there was a good deal of focal round cell infiltration, consisting mostly of plasma cells. Some of these collections were around the blood vessels (figs 3 and 4), but it was not a constant feature Certain blood vessels showed endothelial proliferation, while at the periphery of the lesion new vessels could be seen in great abundance A Levaditi stain failed to reveal the unequivocal presence of spirochetes The pathologic diagnosis was compatible with gumma of the lung

SUMMARY

A case of gumma of the lung is presented, with histologic confirmation The diagnosis was made in a living patient, from tissue removed by lobectomy To my knowledge, such a case has not heretofore been reported The clinical, roentgenologic and pathologic observations are described in detail

A NEW BODY DEODORANT

Its Nonallergenic Properties and Usefulness

THOMAS F B DARNELL, M D

LITTLE ROCK, ARK

UNTIL recently foul odors in hospitals and patients' sickrooms had to be tolerated because no practical means of preventing or eliminating them was known. However, because of the physiologic and psychologic effects of unpleasant odors on patients, hospital personnel and visitors, constant search for a good method of deodorization was being made.

At the time this report was being written, the most practical method of deodorization and the only one to be accepted for promotion through American Medical Association publications was a specially prepared deodorant solution of 12 per cent potassium mercuric iodide, 25 per cent sodium hydroxide and potassium iodide, 0.24 per cent in distilled water¹. As originally introduced for hospital and sickroom deodorization, the solution was used in two ways: 1. If the odor had already escaped into the room, the solution was poured into a specially designed unit which sucked the odor-laden air into the machine, blew it against the solution and then the deodorized air was blown back into the room. None of the solution or any of its active ingredients escaped into the air. Another distinct advantage was the decided reduction in the number of bacteria in the air passing over the solution in the unit². 2. When odors emanate from suppurative surface lesions, burns, osteomyelitis, colostomy openings and the like, they may be effectively combated at their source by placement of a few layers of gauze soaked in the solution over the surgical dressing or colostomy opening. When the odor comes in contact with the moistened gauze it is destroyed and hence cannot contaminate the air³. Both of these methods are satisfactory and convenient. However, it was not possible to use either of these methods to take care of odors originating in axillary folds, regions of the pubis and mammae. In cases of this kind, the deodorant must be applied directly to the cutaneous surface. Deodorizing agents applied to the

Dr H O Lloyd, Jefferson City, Mo., assisted in the study

1 Marketed under the name of aero-klenz®

2 Danforth, T F, Rudig, D M, and Fishbein, W I. Machine and Solution to Control Air Borne Bacteria, Mod Hosp (no 5) 66:100 (May) 1946

3 Schnedorf, J C. An Experimental Investigation of a Deodorant, personal communication to the author

skin must not only be effective but bland, nonirritating and nonsensitizing. Previous search and clinical studies have established the bland and nonirritant properties of this deodorant solution.⁴ The purpose of this investigation was to determine whether the deodorizing solution had any sensitizing properties and at the same time study its effectiveness as a deodorant for personal use. The deodorant solution used in this study (hereafter referred to as deodorant or test solution) consisted of 0.12 per cent potassium mercuric iodide, 0.25 per cent sodium hydroxide and 0.02 per cent potassium iodide in distilled water.

PROCEDURE

This study was carried out on a group of volunteers who were prisoners at the Missouri State Penitentiary, Jefferson City, Mo. One of the prison physicians cooperated in this study. With this cooperation it was possible for the subjects to be kept under almost constant observation. The plan of study was as follows:

On all subjects patch tests were made with the deodorizing solution to be studied before the solution was applied to the body in any other manner. Patch tests remained on patients for forty-eight hours unless otherwise indicated, and at the end of that period the results were observed. Any subject who showed a positive reaction at this time was excluded from further study. Subjects showing any evidence of dermatitis, particularly in the axillary region, which might later be confused with contact dermatitis arising from the application of the solution being tested, were not included in the study. All remaining subjects were instructed to apply the test solution to the axilla twice a day for a period of thirty days, unless otherwise instructed. The subjects were told to report any redness, eruption or increased sensitivity, and when these signs or symptoms developed, to stop the application of the solution. After more than thirty days of application, the subjects discontinued the use of the solution, but after a rest period of approximately one week the subjects were instructed again to apply the same solution to the axillas, this time for three days. At the end of three days the subjects were again examined for the presence of any eruption which might be contact dermatitis or any other dermatitis that might be due to the drugs in the solution. At the same time, all of these subjects were again given patch tests with the original solution. This group included those that had or did not have eruptions at this time and included also those in whom eruption developed before the thirty day period was completed. All in this group who showed positive

⁴ Isenberger, R. M. Investigation of Deodorant Solution, personal communication to the author.

or doubtful reactions to patch tests were, after a lapse of time, given patch tests with six different items. These six patch tests were as follows:

One patch test was made with a 0.12 per cent of potassium mercuric iodide solution, one with a 0.25 per cent sodium hydroxide solution, one with a 0.02 per cent potassium iodide solution. One was made with cloth previously used in the patch test to contain the solution being tested. One was made with the adhesive and cellophane patch test material (elastopatch,^o Duke Laboratories). The remaining patch test was made with the original test solution, containing all the ingredients.

RESULTS

During the study all patch tests that resulted in a doubtful reaction were repeated. It is known that many subjects applied the solution to the axillas in excess of the number of times requested.

*Reaction to Patch Tests (645 Patients)**

Test Material	Positive Reactions
Potassium mercuric iodide solution (0.12 per cent)	1
Sodium hydroxide solution (0.25 per cent)	3
Potassium iodide solution (0.02 per cent)	1
Cloth used with solutions	0
Adhesive and cellophane †	0
Test solution with all ingredients	7

* One subject showed a positive reaction to the test solution, solution of sodium hydroxide and also potassium mercuric iodide.

† Slightly positive reactions to adhesive tape were not recorded. No reactions here were positive enough to be confused with positive reactions to other test materials.

Three subjects, during the study, presented an axillary eruption thought to be contact dermatitis. Only 1 of these 3 showed a positive reaction to a patch test. This subject showed a positive reaction to the test solution and to sodium hydroxide solution. Two subjects showed an acneiform eruption scattered over the trunk and arms but had negative reactions to all patch tests. Two subjects gave a history of a generalized eruption after two weeks of application of the test solution. The history suggested urticaria. The reactions in these cases were negative to all patch tests. The presence of atopy or other allergies in the subject or in his family evidently had no relationship to the allergic reaction to the test solution studied. At any rate, most of the subjects with histories of allergies or a family history of allergy showed no evidence of an allergic reaction to the test solution.

DEODORIZING PROPERTIES

All subjects were questioned individually regarding the efficacy of the solution in destroying the odors from the perspiration of the axilla.

Questioning was done at the end of the thirty day period during which time the subjects applied the solution twice a day. Results were as follows

Total number of subjects	645
Number who stated that the odor was stopped	512
Number who stated that no change was noted	34
Number who stated that the odor was decidedly decreased	82
Number indifferent to presence or absence of odor	17

It must be remembered that the test solution was usually applied not more than twice daily. It is entirely logical that the prisoners, during excessive work, lost much of the solution from their body during the interim between applications. Also, it must be taken into consideration that not all prisoners were honest in their application. These facts must be taken into consideration before evaluation of the deodorizing effect. Many subjects during this study evidently used the test solution much more than twice a day, since many repeatedly called for refills of their bottles, making particular mention of the fact that they wanted the solution to kill perspiration odor. At the beginning of the study subjects were not told that the solution would cancel odors, but were asked to note whether the solution deodorized, stopped or made odors worse.

CONCLUSIONS

1 The product tested, containing 0.12 per cent potassium mercuric iodide, 0.25 per cent sodium hydroxide and 0.02 per cent potassium iodide, is, according to this study, relatively nonsensitizing when applied to the human body. The mercurial ingredient of the solution is evidently nonsensitizing as compared with other mercurial preparations.

2 This solution may be applied to the skin over long periods of time with little danger of the development of allergic reactions.

3 This solution, in my opinion, has a definite deodorizing quality and could well be the answer to a physician's need for a deodorizing medicament.

804 North Van Buren Street

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

David Bloom, M D, *President*

Henry Silver, M D, *Secretary*

March 21, 1946

A Case for Diagnosis (Chronic Erythroderma with Generalized Lymphadenopathy? Lymphoblastoma?) Presented by DR CHARLES PINES

C D, a laborer aged 63, born in Bohemia was admitted to the Department of Dermatology and Syphilology of the Third Medical (New York University) Division, Bellevue Hospital, service of Dr Frank C Combes on March 18 1946, because of generalized erythroderma associated with generalized lymphadenopathy. The cutaneous eruption began about two years ago and gradually spread over the entire body.

The skin is considerably thickened and bluish red with deep furrows and gyrate patches. There are numerous excoriated lesions scattered over the body as a result of intense itching and scratching. In the inguinal and femoral regions there are huge masses of matted lobulated lymph nodes, some show postoperative scars.

The Wassermann reaction of the blood was negative. The examination of the blood revealed no significant abnormal changes. Examination of the urine showed albumin. Histologic examination of a specimen of the skin showed chronic non-specific dermatitis. Histologic examination of a cervical lymph node revealed chronic nonspecific adenitis.

DISCUSSION

DR MARION B SULZBERGER. This case is unusual in the degree of changes, with respect to both the lichenification of the skin and the enlargement of the lymph nodes. I do not recall having ever seen a case with such huge, such gigantic and such generalized lichenification and nodes. I have no suggestions regarding the diagnosis beyond the fact that it is an erythroderma with lymphadenopathy. I would like to ask whether any of the members have had experience with cystine or other thiol-containing amino acids in the treatment of such eruptions. There have been reports from England of beneficial effects from cysteine and cystine.

DR LEO SPIEGEL. My co-workers and I see these cases frequently at the Bellevue Hospital and we call them "Bellevue disease." They present generalized erythroderma associated with enlarged glands. I have never seen a patient with glands as large as in the case presented. At times one observes sarcomatous changes. In the last issue of the "Year Book" a series of 12 cases of this type is discussed by a Swedish author (C Bruck, Stockholm, Year Book of Dermatology & Syphilology 1945 p 540). It appears that this disease frequently occurs in Sweden. In most of these cases tuberculosis develops as the erythroderma progresses.

The author offers no suggestions with respect to therapy. A patient whom I have treated with cystine hydrochloric acid, 1 Gm daily, has thus far shown no improvement. The pruritus was intense, and examination of the blood showed 16 per cent eosinophils. These patients usually show a high degree of eosinophilia.

DR HERMAN SHARLIT Many of these conditions turn out to be a reaction to an irritant, and in these cases, if the condition is diagnosed, a cure can be obtained. This fact should never be overlooked. Spectacular improvement may occur in some persons when they are removed from their environment.

DR MARION B SULZBERGER Dr Sharlit's remarks are well taken. I have seen cases of exfoliative erythroderma with lymphadenopathy which were later actually found to be cases of contact type dermatitis, but which no clinical or histologic studies could distinguish from other forms of generalized erythroderma. One man, a tailor, had a generalized red and exfoliating eruption, itching intensely with deep pigmentation in many areas, of long standing and with decided enlargement of the lymph nodes. Dr Kadish at Montefiore Hospital proved that it was due to a dye in the materials with which the patient came into contact. In this case all the required criteria for the diagnosis of contact dermatitis were satisfied. My co-workers and I were originally unable to distinguish clinically between the disease in that case and the erythrodermas of mycosis fungoides, blood dyscrasias, psoriasis, lymphoblastoma or tuberculosis.

DR CHARLES PINES Histologic examination of a cervical lymph node showed chronic lymphadenitis. The condition in this case impresses one as belonging to the lymphoblastomas. In about 25 per cent of these cases the disease is transformed into one of the types of lymphoblastoma, and I suspect strongly that this will occur in my case. The possibility of contact dermatitis was not overlooked. The blood and biopsy specimens of the skin and lymph nodes will be repeatedly studied.

Erythroderma Associated with Giant Follicular Lymphadenopathy Presented by DR CHARLES PINES

S. H., a fur dyer aged 52, was admitted to the Department of Dermatology and Syphilology of the third medical (New York University) Division, Bellevue Hospital, service of Dr Frank C. Combes, on Sept 12, 1945, because of a moderately pruritic erythematous generalized eruption of a few months' duration. The past history was irrelevant.

The cutaneous eruption began on the lower extremities about three years ago. At the onset the response to local therapy was satisfactory. There were remissions and exacerbations. In the past few months the eruption gradually became worse and spread over the entire body with the exception of the scalp.

The entire integument, the scalp excluded, is thickened and dusky red. In some areas there is considerable lichenification and fissuring. The skin is covered with thin flaky loosely adherent yellowish scales. There is moderate lymphadenopathy in the inguinal and femoral regions, especially on the right side. The lymph nodes are firm, slightly tender on palpation, and the covering skin is freely movable.

The Wassermann reaction of the blood was negative. Examination of the blood showed slight secondary anemia with 3 to 5 per cent eosinophils. Roentgenographic observations of the chest were normal. Fungi were not found in the scrapings from the skin. Examination of the urine showed albumin (3 plus) and a few waxy casts. Patch tests with fur dyes were not made because of the general condition of the skin.

Histologic examination of an axillary lymph node revealed a moderately thick fibrous capsule covering the lesion. The follicles were hyperplastic, and the germinal centers were large and contained large mononuclear cells. The pulp substance contained lymphocytes, plasma cells and a moderate number of large mononuclear cells. There was moderate fibrosis present. Some areas showed collections of eosinophils and polymorphonuclear cells.

DISCUSSION

DR LEO SPIEGEL. The case is similar to the one just discussed. The difference is only one of degree. One is of three and the other of sixteen years' duration. The case is most unusual.

DR CHARLES PINES. The histologic observations in this case differ from those in the first case. This case showed distinctly the pathologic entity described under various titles by Symmers and others. The association of the cutaneous manifestations with the pathologic entity is not clearly understood. Contact dermatitis, chronic discoid lichenoid dermatitis or one of the exfoliative type of erythrodermas may present this picture in association with giant follicular lymphadenopathy.

Lupus Erythematosus Associated with Lupus Pernio Presented by Dr
CHARLES WOLF

A P., a woman aged 48, a Portuguese by birth, residing in the United States for the past twenty-five years and the mother of four children, about five years ago had an eruption on the flush areas of the face, forehead and scalp. The patient has been treated at various institutions with little benefit.

At present there is an erythematous area on the tip of the nose with dilated plugged sebaceous ducts. The left cheek shows a scar from a biopsy. On the scalp there are several atrophic areas with some of the patulous ducts still visible. The distal phalanges of most of the fingers of both hands show an erythematous swelling. In cold weather the swelling is somewhat larger and more painful.

The Wassermann reaction of the blood was negative. Roentgenograms of the lungs showed several fibrocalcific infiltrations in both apical regions. The appearance was that of an old tuberculous process. Roentgenographic observations of the bones of the hands were normal. During the past year the patient has received about fifty injections of liver extract and 1,000 mg of ascorbic acid daily.

DISCUSSION

DR HERMAN SHARLIT. Did the butterfly lesion disappear as a result of treatment with liver and ascorbic acid?

DR HENRY SILVER. What type of lupus pernio is the diagnosis in this case? I ask this question because we must differentiate between the Hutchinson and the Besnier types. The name lupus pernio applies to both, but the clinical and especially the histologic pictures presented by each differ. The Besnier type is considered by most observers as sarcoid, while the Hutchinson type or chilblain lupus is a variety of lupus erythematosus. Dr Wolf's case is an excellent example of chilblain lupus. Here one frequently sees tumefied lesions on the nose and fingers which become aggravated during cold weather.

DR DAVID BLOOM. To me the lesions on the scalp appear to be the end stage of folliculitis decalvans rather than lupus erythematosus. Furthermore, the lesions on the face and on the fingers, I believe, cannot be diagnosed correctly without microscopic examination.

DR CHARLES LERNER Has the patient been given injections of gold compound at any time?

DR CHARLES WOLF In reply to Dr Sharlit, I do not presume to say that the result of treatment given has cleared the butterfly lesion, but at least the patient has been benefited. There is a question as to whether it would have cleared spontaneously. As to lupus pernio, I apply the diagnosis to the lesions on the fingers. The lesions of the face showed no change in winter, but the fingers, on the other hand, become tender and cyanotic in cold weather. I agree with Dr Silver's view that this is the lupus erythematosus syndrome and not the Besnier type. In answer to Dr Lerner, the patient has received gold and bismuth compounds at various institutions. However, the treatment I employed proved beneficial.

**Dermatitis Medicamentosa of the Bullous Erythema Multiforme Type
from Phenobarbital** Presented by DR CHARLES WOLF

Macular Atrophy with Lesions on the Face Presented by DR PAUL GROSS

David Bloom, MD, *President*

Henry Silver, MD, *Secretary*

April 18, 1946

**A Case for Diagnosis Erosions of Umbilical Region, Histologically
Lymphoblastoma (Pemphigus? Lymphoblastoma?)** Presented by
DR LOUIS CHARGIN

Lupoid Sycosis Presented by DR WILBERT SACHS

L. S., a man aged 45, has been suffering from an eruption on the face for the past twenty-five years. He received considerable treatment without benefit. He never was entirely free of lesions, but, at times, improved for a month or two.

The process begins with papules and pustules. Above the ears, on the bearded area of the cheeks, on the chin and on the lips is an erythematous papulopustular eruption. There are many scars, and most of the hairs are lost. The Wassermann reaction of the blood was negative. During treatment with penicillin ointment new lesions failed to appear.

DISCUSSION

DR HENRY SILVER I cannot agree with Dr Sachs's diagnosis of lupoid sycosis. It seemed to me, on gross examination, that this is sycosis vulgaris. What is accepted as lupoid sycosis is a severe form of the disease, associated with central atrophy and advancing pustular border, factors absent in this case. In addition, lupoid sycosis is recalcitrant to any form of therapy, including penicillin ointment. In regard to penicillin ointment in sycosis, I would say that some cases respond and, when they do, they do so dramatically. In some cases, however, the condition recurs in spite of initial benefit, exactly as has been the experience with other forms of therapy, including quinolor® ointment (contains 10 per cent benzoyl peroxide and 0.5 per cent quinolor [a mixture of three chlorine derivatives of 8-hydroxyquinoline] in a base of equal parts of petrolatum and wool fat).

DR LOUIS CHARGIN I think that a histologic examination should be made

DR. DAVID BLOOM This is a case of lupoid sycosis. The temporal region is a favorable location. From here the folliculitis and the alopecia may extend to the whole circumference of the scalp.

DR. CHARLES R. REIN I should like to warn against the indiscriminate use of penicillin ointment in this type of disease, since sensitization often develops if this medicament is applied over a long period.

DR. LEO SPIEGEL I certainly would not make the diagnosis of lupoid sycosis because of the absence of papular and pustular lesions. There is no evidence of activity at present, and some aspects suggest lupus erythematosus.

DR. WILBERT SACHS My reasons for the diagnosis of lupoid sycosis were the duration of over twenty-five years, the scarring, the loss of hair and the presence of lesions above the ears. I did not intend to stress the beneficial effect of penicillin ointment in this case.

Pustular Acneform Eruption due to Iodide Salt Presented by DR. VAN ALLSTYNE CORNELL

J. W., a Negro aged 28, obtained from a druggist a "tonic" containing potassium iodide. He began taking the medicine one week previously. After four days there developed on the forehead, cheeks, nose and chin pustules on an erythematous base the size of a pinhead or a pea. There were no subjective complaints. After the discontinuance of treatment with the tonic the eruption began to clear.

DISCUSSION

DR. FRANK E. CROSS This man has taken the drug for only four days and presents a typical iodide eruption. This would indicate that he is rather sensitive to small amounts of the drug.

DR. MAX BERKOVSKY I wonder whether anyone here has had any experience with cases of severe acne that were found in the Army, especially in some of the men who come from the Pacific Theater. It is my impression that the acneform eruption is caused by one of the halogen group, probably by the chlorinated water used in war theaters. These patients recover rather rapidly when they return to the United States.

DR. DAVID BLOOM Had this patient taken iodides at any previous occasion?

DR. LOUIS CHARGIN It seems to me that the halogens do not act in the same way as other drugs with respect to allergy. The action is cumulative. Even sensitive persons have to take the drug for prolonged periods, at least for a number of days before the eruption appears, and a relatively small dose will not cause this reaction. However, there are exceptions. Some years ago I observed a patient with Huntington's chorea treated with iodides who reacted violently to the smallest dose exhibiting severe coryza, salivation and suffusion of the eyes. I do not believe that the acute type of reaction is observed in the case of bromides.

DR. MARION B. SULZBERGER In answer to Dr. Berkovsky's question about acne in military personnel in the tropics, I was fortunate in having an excellent opportunity to study these cases. It was most interesting to note that on Guam the severe acneform dermatoses accounted for as many cases of morbidity and disability as did fungous infections. The detailed studies will shortly appear in *Naval Medical Bulletin*. Two patients with tropical acne were placed first in the usual wards, without special therapy. During this period Dr. Kendall Emerson

studied their chloride excretion, blood chlorides and the water intake and output, and I watched the course of their dermatosis. As expected, the eruptions showed no change. The other patients with the same type of eruptions were placed in an air-conditioned ward, but with the same diets and the same type of water and without treatment. Within ten days 1 man improved about 75 per cent and the other about 50 per cent. This improvement took place just through the reduction of the environmental temperature and the relative humidity. There is no doubt that great numbers of these cases of acne occurred in many places with exceptionally hot humid environment. The condition occurred in men working on deck watches and those working below, in office personnel, in men living in good quarters under the best and cleanest conditions, as well as in those in combat and bivouacked under the most difficult hygienic conditions, in officers and in enlisted men. The only factor in common was the protracted stay in places with high degrees of heat and humidity. While it has not been proved, everything seems to point to the conclusion that these cases are due to the constantly moist skin surfaces, the plugging up of the pilosebaceous orifices, the keratin swelling and the consequent damming up of secretions. This process would be similar to that causing prickly heat, which is now believed due to the plugging of the sweat pores.

In answer to Dr. Chargin, nobody knows the exact mechanism of the iodide eruptions. It is true, however, that one sees cumulative effects in eruptions due to other drugs, but I believe that the observations of cumulative action may be somewhat commoner in eruptions due to halogens. On the other hand, there are many eruptions due to iodides and bromides with clear evidence of exquisite hypersensitivity, in which a single exposure to a minute quantity suffices to elicit severe and long-lasting eruptions.

DR CHARLES WOLF. I wonder whether the explanation might not be made on a different basis. In the tropics one perspires so profusely that the water metabolism is disturbed to such an extent that the chlorides are excreted through the skin. They become irritants, thus causing the eruption.

DR MARION B. SULZBERGER. I think that Dr. Wolf's remarks are tenable, but I do not want to say that this is the only possible mechanism that can produce plugging of the follicular openings.

Scleroderma in a Child Presented by DR. DAVID BLOOM

A Case for Diagnosis (Lichen Planus? Linear Nevus?) Presented by DR. CHARLES R. REIN

Lichen Planopilaris Presented by DR. CHARLES R. REIN

N. K., a white married woman aged 41, presents an eruption on the trunk, flexor areas of forearms and oral mucosa of five years' duration. The lesions on the flexor surfaces of the wrists and in the mouth are typical of lichen planus. She also presents an irregularly annular, sharply margined lesion below the right breast. The border is definitely infiltrated, while in the central portion there are several small inflammatory papules. This lesion, however, has flattened considerably following one roentgen exposure (75 r).

In addition, the patient presents several patches varying in size from that of a dime to that of a quarter. They are situated on the left shoulder and over the right scapula and appeared about three months previously. Similar, but less well defined, patches are present on the anterior aspect of the left thigh and the lateral aspect of the right thigh, these are of five years' duration. The patches

consist of discrete flesh-colored pinhead-sized acuminate papules with a central horny comedo-like plug which can be readily expressed. After injections of bismuth subsalicylate some improvement was noted.

DISCUSSION

DR WILBERT SACHS This is a good illustration of lichen planopilaris. The interesting thing to me is that the patient had lichen planus for several years before the follicular lesions developed. I am not sure that lesions may not eventually develop on the scalp.

DR LEO SPIEGEL A patient under my observation, a youth of 18 years, had a more widespread eruption than this woman. Associated with the eruption were patches of alopecia on the scalp. Dr Sachs made the diagnosis of lichen planopilaris microscopically. Clinically, there was a suggestion of atrophy, which the histologic examination failed to show.

DR DAVID BLOOM The lesion under the breast appears to be superficial basal cell epithelioma.

DR MAURICE UMANSKY The eruption consists of two types of lesions. In some areas one sees flat-topped papules of lichen planus. In other areas there are follicular acuminate spinous lesions. The eruption, therefore, fits in well with the variety of lichen planus which Pringle designated as lichen planopilaris. Pringle stated that it was incorrect to label such conditions as lichen planus because of the presence of acuminate lesions. Dr Sachs lately appropriated this name for lichen planus in which alopecia and follicular lesions occur also on the scalp (Feldman's lichen planus et acuminatus atrophicans).

DR FRANK E. CROSS I cannot agree with Dr Bloom's diagnosis with respect to the lesions under the breast. I believe these to be lichen planus. The lesions here are apparently macerated.

DR HENRY SILVER The case is typical of the disease. The name lichen planus et acuminatus atrophicans suggested by Dr Feldman is the most appropriate for this disease.

DR CHARLES WOLF This patient has lichen planus with definite manifestations of the disease. She has the real coalescent flat papules which have formed plaques. She has the acuminate lesions on the shoulder and atrophic lesions under the breasts. These are all manifestations of lichen planopilaris.

DR CHARLES R. REIN The majority of lesions are characteristic of lichen planus. Although the lesions under the right breast resemble basal cell epithelioma, they showed 50 per cent involution within one week following an exposure to $\frac{1}{4}$ skin unit of roentgen rays.

Wilbert Sachs, M.D., *President*

Henry Silver, M.D., *Secretary*

Nov 21, 1946

Epidermolysis Bullosa Hereditaria Treated with Antireticular Cytotoxic Serum. Presented by DR CHARLES R. REIN

C. P., a native born white girl aged 8 years, is presented primarily to determine the effect of antireticular cytotoxic serum therapy. The patient had been studied previously at numerous clinics throughout the city.

The eruption began at birth and has persisted with alternating periods of remission and exacerbation. The child's mother gave an identical history of lesions which began at birth, but to a lesser degree than in the child.

The patient was first seen on July 26, 1946, at which time she presented bullae and vesicles scattered over the palms, the sides of the feet and the knees, some bullae were hemorrhagic

On August 29, 0.02 cc of antireticular cytotoxic serum (rabbit) was administered subcutaneously. There was no local or systemic reaction. On September 3, 0.05 cc of the serum was given. Twenty-four hours later the patient presented a reaction at the site of injection, consisting of an erythematous, edematous area the size of a silver dollar with vesicles and bullae at the border of the lesion. Associated with it was a systemic reaction manifested by malaise and rise of temperature to 102 F. On September 6, 0.02 cc of antireticular cytotoxic serum (rabbit) was given in the right arm and antireticular cytotoxic serum (goat) in the left arm. There developed a systemic reaction within twenty-four hours after the injection.

Similar antireticular cytotoxic serum material was administered to 3 other apparently normal subjects, and little or no local reaction was observed.

The mother stated that the condition cleared up almost completely following any moderate febrile episode. Similar improvement was noted following the febrile episode caused by the antireticular cytotoxic serum.

DISCUSSION

DR ARTHUR SAYER: Is the antireticular cytotoxic serum intended as a therapeutic procedure?

DR MARION B. SULZBERGER: As a rule, when reactions are produced by repeated injections of serum derived from species foreign to man, whether from goat, rabbit or horse, these reactions are due to the antigenic property of the serum of the foreign species. The interesting thing, however, is that a given foreign serum is not quite as antigenic as is the "immune" or "antibody-containing" serum of the same species. One might, therefore, expect that the antibody-containing antireticular cytotoxic serum would have strong antigenic properties. The accelerated response mentioned in this case is, of course, the classic one that Schick and von Pirquet described as a cardinal manifestation of foreign serum allergy, so I would venture to predict that this patient will be found to have been sensitized to rabbit serum and will react to skin tests with rabbit serum.

DR MAX JESSNER: When I first saw the patient, she presented, apart from the epidermolysis bullosa, a picture that resembled dermatitis herpetiformis. She did not react to potassium iodide internally, but the bullae showed 70 per cent eosinophils. This disease may belong to the type which may be placed between dermatitis herpetiformis and epidermolysis bullosa and which was discussed by Jadassohn at the Hamburg Congress of the German Dermatological Society in 1921 (*Arch f Dermat u Syph* **138** 463). Another possible diagnosis to be considered because of the lesions on the neck is Hailey-Hailey's disease. Permission for a biopsy could not be obtained.

DR CHARLES R. REIN: I agree with Dr. Sulzberger that the unusual bullous reactions which developed in this patient at the site of the injection of antireticular cytotoxic serum were of the nonspecific type. Similar reactions should be expected following the injection of any substance capable of producing a severe local inflammatory reaction.

Lymphoblastomatous Nodules in Areas of Acrodermatitis Chronica Atrophicans Presented by DR CHARLES R. REIN

Xanthomatous Lesion in Acrodermatitis Chronica Atrophicans Presented by DR FRANK E. CROSS

Syringoma Presented by DR CHARLES WOLF

Lupus Erythematosus Responding to Suramin Sodium (Naphuride®)
Presented by DR MARION B SULZBERGER and (by invitation) DR VICTOR H WITTEN

H R, a man aged 49, presents an eruption of the face which first appeared on the cheeks and tip of the nose in 1938. The clinical and histologic diagnosis in 1939 was lupus erythematosus.

Since the onset of the eruption the patient has had the following treatment: one course of bismuth subsalicylate in oil, twenty-seven biweekly to weekly injections for a total of 45 mg intramuscularly, one course of gold sodium thiosulfate, five weekly injections for a total of 46 mg intravenously, a second course of gold sodium thiosulfate for a total of 45 mg, sulfapyridine 0.5 Gm twice daily for a total of 45 Gm, quinine sulfate $7\frac{1}{2}$ grains (0.49 Gm) twice daily and lesions painted with tincture of iodine twice daily for a total of three weeks' treatment, nicotinic acid, 50 mg four times a day for two weeks, sulfathiazole 0.5 Gm twice daily for two months for a total of 90 Gm, sobisminol, 2 capsules twice a day for two months, sulfadiazine 0.5 Gm twice daily for approximately two months for a total of about 90 Gm, a third course of gold sodium thiosulfate, twelve injections, for a total of 230 mg, oxophenarsine hydrochloride, fourteen injections intravenously, for a total of 415 mg, and a fourth course of gold sodium thiosulfate, six injections, for a total of 55 mg. Locally, many therapeutic measures were used, including destructive procedures such as solid carbon dioxide and electrodesiccation, gold sodium thiosulfate preparation injected locally and penicillin ointment.

The only definite favorable response to treatment occurred during the first course of bismuth compound, when the lesions appeared lighter and somewhat less infiltrated. The patient was seen again on Oct 26, 1946, after having last been seen in April when electrodesiccation and curettage were performed. He then presented on the left cheek, at the anterior and inferior borders of the roughly triangular, depressed, scarred area, two roughly circular, fairly well defined, erythematous, dry lesions the size of lima beans, each of which had an elevated, moderately infiltrated border and a slightly depressed, lighter center. A similar lesion the size of a nickel was noted just anteroinferior to the right ear, with two lesions the size of peas immediately below. There was slight swelling of the involved area of the right cheek. On the mucous membrane of the mouth at the external border of the lower gingiva, there was an eroded patch, 1.0 by 0.2 cm, covered with a light tan pellicle. Just anterior to this there was a similar lesion the size of a pinhead.

On October 26, 0.25 Gm of suramin sodium (naphuride®) was given deeply intramuscularly. One week later the oral lesion had disappeared and 0.5 Gm of suramin sodium was again given intramuscularly.

Two weeks after the first injection of suramin sodium the lesions on the face were somewhat less erythematous, with diminished infiltration and edema. With this visit 0.75 Gm of suramin sodium was given.

When seen a week later (November 16) the lesions were definitely less erythematous, with diminished infiltration and edema. Because of a febrile generalized reaction from the previous injection, only 0.5 Gm of suramin sodium was given at this visit. Coincident with the improvement of the facial lesions, the patient stated that chronic rectal discharge (which apparently followed a hemorrhoidectomy in 1939) was decidedly improved for the first time since its onset. The last injection was again followed by a mild febrile reaction.

DISCUSSION

DR MAURICE UMANSKY Recently a number of cases of lupus erythematosus were presented elsewhere in which suramin sodium was used. The reported results were favorable. The dosage was much smaller, about one tenth of the dose given in this case. The advantage of smaller doses is evident, since suramin sodium is a highly toxic drug, especially to the kidneys. Smaller doses are liable to produce less toxic reactions proportionately.

DR RUDOLF L. BAER This patient did not have any treatment for a considerable period prior to the administration with suramin sodium. The speed of the improvement was remarkable and became evident after the second injection. The question arises as to whether the remarkable improvement which is now present is due to the febrile reactions which occurred after the third and fourth injections. This is not likely, since the improvement was rather definite before the third injection was given.

DR ARTHUR SAYER The patient stated that the last treatment benefited him most. Should suramin sodium be the drug of choice or should the standard remedies, such as bismuth or gold compounds, be given a trial first?

DR FRANK E. CROSS The patient stated that compared with previous treatment suramin sodium gave the best result. At the Mount Sinai Clinic, where considerable experience was accumulated with suramin sodium in lupus erythematosus, the drug is given in an average of about eight weekly intramuscular injections, followed by a rest period. The course is repeated according to need. The reactions which the drug produces may be of benefit. Because of the possibility of nephritis, one should begin with small doses. Schamberg obtained as good results with smaller doses of gold sodium thiosulfate as he did with larger doses. Needless to state, one should use the dose that will give the best therapeutic effect with the least possible toxic effect.

DR MARION B. SULZBERGER Many of us have had considerable experience with this drug. Under the names germanin® and bayer 205® it was widely used after the first world war. I have used suramin sodium for almost twenty years, have treated many different diseases with it and today still consider it the treatment of first choice in pemphigus. Suramin sodium is "toxic," but in my opinion its toxicity has been overemphasized. Naturally, like most potentially toxic and sensitizing drugs, suramin sodium must be given with caution, with knowledge and in proper doses. In a recent issue of *The Journal of the American Medical Association* the dosage schedule is given as 10 Gm per week. I agree with Dr. Cross that one should begin with smaller doses, 100 to 200 mg, increasing the dose only if and when necessary. I hold that this rule should apply not only to suramin sodium but also to drugs such as arsenicals and gold salts. It is my opinion that gold sodium thiosulfate is by no means the best gold preparation to use in lupus erythematosus, the organic compounds, such as solganol-B oleosum® (aurothioglucose suspended in oil), chrysolgen® (4-amino-2-aurothiopenol carbonic acid) and triphal® (sodium aurothiobenzimidazol) are to be preferred because of their lower toxicity in therapeutic doses. I believe that gold may be as dangerous as suramin sodium, and it has produced erythrodermas, blood dyscrasias, hemorrhagic states and deaths. It is unfortunate that physicians who began treating arthritis with gold compounds utterly failed to profit by the complete and extensive dermatologic experience and continued using large doses, which dermatologists had long since abandoned and reported as dangerous. It is only recently that the internists are using better gold compounds and safer dosage schedules.

In previously untreated chronic discoid lupus erythematosus I now first try bismuth compound, usually bistrimate® (bismuth sodium triglycollamate) by mouth,

or oily suspensions of bismuth by intramuscular injection, if this fails I use gold in small doses (but organic gold preparations, not gold sodium thiosulfate) As additional remedies I employ o-phenarsine hydrochloride and suramin sodium

I have seen only a small series of cases of lupus erythematosus treated with suramin sodium The results have been good so far I think that it is another drug worth trying in refractory cases

NOTE—The patient here presented had a prompt and extensive recurrence of the facial lupus erythematosus within a week after the cessation of treatment with suramin sodium As his urine had albumin and a few casts and since the suramin sodium had produced so short a remission, it was decided to try ethyl chaulmoograte by injection

Pemphigus Vulgaris of Five Years' Duration Presented by DR DAVID B BALLIN

Treatment with dihydrotachysterol was of no benefit Treatment with acetarsone, because of intolerance, had to be discontinued after a few doses Lesions dry quickly after baths with potassium permanganate or local application of a solution of potassium permanganate

DISCUSSION

DR FRANK E CROSS I recall a patient with pemphigus presented before this society who had had the disease for about eight years The lesions have lately assumed the character of pemphigus foliaceus I believe that the case presented tonight, because of its long duration, may also eventually terminate in pemphigus foliaceus

DR HENRY SILVER In the past few years a number of cases of pemphigus vulgaris were presented before this society which responded to a variety of treatments Dr Wolf, Dr Rein and now Dr Ballin reported cases in which they had given treatment for over five years I wish to add a patient under my observation A woman aged 54 originally presented a widespread typical eruption with oral and vaginal lesions Now, after four years, there is only one triangular area on the chest in which crops of bullae recur This patient responded well to treatment with acetarsone, liver injections, riboflavin and iron

DR CHARLES R REIN At a previous meeting I presented a patient with a few bullous lesions involving the scalp and oral mucosa He recently had a fifth exacerbation, which is again responding to suramin sodium therapy My patient is receiving 1 Gm three times a week and seems to be tolerating it well I agree with Dr Sulzberger that the toxicity of this drug is exaggerated

A Case for Diagnosis (Lingua Geographica?) Presented by DR MARION B SULZBERGER and (by invitation) DR GDALI RUBIN

Granuloma Inguinale in the Fossa Navicularis Urethrae Presented by DR CHARLES PINES

DISCUSSION

DR CHARLES PINES I would be interested in opinions as to whether the disease is contracted through sexual intercourse Further, whether the morphologic features of the Donovan bodies and the therapeutic response to antimony potassium tartrate point to the protozoon nature of the causative agent

DR NATHAN SOBEL It is rare to see granuloma inguinale confined to the urethral meatus This is the first case I have seen in this location It is further

of interest that the patient presents no symptoms, although he may eventually have an obstruction of the urethra from the healing of the lesion. Whether granuloma inguinale is a venereal disease has not yet been settled. In many cases it is transmitted by sexual contact, but it may in some cases be transmitted by a vector such as the louse. While the organism has been cultured, I do not believe that it has as yet been classified. It may prove to be either a protozoon or a bacillus. Not infrequently one sees small persistent lesions on the genitals in which a clinical diagnosis of a primary lesion is made and in these lesions Donovan bodies are often demonstrated.

DR CHARLES R. REIN: Although the incidence of pediculosis pubis is relatively low in Negroes, many Negroes with granuloma inguinale have or have had pediculosis pubis. Is the louse a vector in the transmission of this disease?

DR FRANK E. CROSS: Dr. Pines has made an excellent diagnosis at such an early stage. Ordinarily one has to see a more extensive involvement before arriving at the diagnosis. Better laboratory technic and an awareness of the possibility of granuloma inguinale while reactions to other tests, such as Ducrey, Frei and dark field, are negative, account for the early diagnosis.

DR RUDOLF L. BAER: The work referred to by Dr. Sobel was done by Anderson, Goodpasture and DeMonbreun, who cultured the micro-organism in the yolk and yolk sac of developing chick embryos. They prepared a washed bacterial suspension, a yolk sac filtrate and a mucoid capsular material and were able to show that those elicited apparently specific cutaneous reactions in patients who had been infected with granuloma inguinale (*J. Exper. Med.* **81**: 25-50, 1945).

DR CHARLES PINES: Scrapings did not show the presence of Donovan bodies. They were, however, demonstrated without difficulty in the histologic sections.

Granuloma Annulare Presented by DR RUDOLF L. BAER and (by invitation) DR MEYER HANTMAN

Boeck's Sarcoid Presented by DR VAN ALSTYNE H. CORNELL

Sarcoidosis with Involvement of the Skin and Lungs Presented by DR PAUL GROSS

Pruritus Apparently Associated with Proximity to Arsenicals Presented by DR NATHAN SOBEL

F. H., a woman aged 40, has been a nurse in the Social Hygiene Clinic of the New York City Department of Health for the past ten years. She was assigned to the preparation of solutions of arsenicals used for antisyphilitic therapy. For the first time, about four weeks ago, she experienced a severe itch while mixing the arsenicals. Since then she has been troubled with generalized itching which appears as soon as she enters the room where the arsenical solutions are prepared, persists while she is there and disappears soon after she leaves the room. When there are no arsenical preparations exposed to the air in that room she does not have the sensation, but as soon as an ampule of an arsenical drug is opened the pruritus recurs. She has had no cutaneous lesions.

On Nov. 19, 1946, patch tests with solutions of arsenicals were applied and read in forty-eight hours. A generalized itch resulted ten minutes after application and persisted until the patches were removed. Oxophenarsine hydrochloride gave no reaction. Whole arsphenamine and neoarsphenamine gave doubtful positive reactions.

Examination of the blood on November 21 showed 86 per cent hemoglobin, 4,500,000 red blood cells and 11,600 white blood cells, with 47 per cent polymorphonuclear cells, 50 per cent lymphocytes, 2 per cent eosinophils and 1 per cent basophils

DISCUSSION

DR MARION B SULZBERGER I have seen several cases which I think may be similar to this one, and most of them were in nurses or doctors working in venereal disease clinics I reported such a case many years ago in a nurse who had itching and urticaria whenever she mixed arsphenamine, eventually she became so sensitive that just going into the room in which the mixing had been done would cause a reaction Finally, she also got typical asthma immediately on entering this room In scratch tests she gave one of the biggest wheal reactions that I have ever seen, in the tests with dilute neoarsphenamine, so dilute that it produced no reaction at all in controls The wheal was so big that when I tested her on the forearm by scratch, the wheal grew, occupying the entire flexor surface of the forearm, then sent out pseudopods which ascended up the bicipital sulcus to the axilla, within a few minutes she had a severe constitutional reaction This nurse had to give up her original duties and had to be shifted from the department and rooms where the arsenicals were mixed This girl's serum contained no passive transfer antibodies to the neoarsphenamine or to conjugates which we made with protein and neoarsphenamine and arsphenamine At that time I believed there was no such thing as a passive transfer to a simple chemical or drug, but since then I have seen at the New York Post-Graduate Medical School and Hospital, a case in which there was an unequivocal, strong, passive transfer of urticarial sensitivity to a sulfonamide drug Feinberg in Chicago (*J Allergy* **16** 209 [Sept] 1945) and Kern in Chicago (*J Allergy* **10** 164 [Jan] 1939) reported that they had serum that would passively transfer hypersensitivity to simple chemicals (chloramine and phthalin anhydride, respectively) The serums which these investigators sent me did not transfer in my tests, and when I reported my negative results, they said that they too were no longer able to transfer with these serums It appears to me that these rare antibodies to simple chemicals are delicate, not nearly as stable as the common Prausnitz-Kustner antibodies to "protein" allergens From the history of Dr Sobel's patient, I would think that there is a better chance of getting a good wheal reaction to scratch or intracutaneous tests than there is of a positive eczematous reaction to a patch test

NOTE—When the patient was subsequently unwittingly exposed to an open container with neoarsphenamine solution, itching promptly occurred

Wilbert Sachs, M D, *President*

Henry Silver, M D, *Secretary*

Jan 16, 1947

Lepra in a Puerto Rican Man Presented by DR VAN ALSTYNE H CORNELL and (by invitation) DR ARTHUR J PHILLIP

Incontinentia Pigmenti Presented by DR NATHAN SOBEL

A T, a Chinese female infant aged 2 years, was seen at the clinic of the Beekman Downtown Hospital The condition has been present since birth Over the entire body, but much less evident on the face, there is a conspicuous pigmentary disturbance characterized by extensive areas showing hyperpigmentation There are also many small areas of hyperpigmentation which assume various shapes The arrangement of these areas result in a bizarre pattern

Except for suppurative adenitis, the infant had no illnesses. The mother and two brothers show no abnormalities of the skin. The father is said to have since birth a similar pigmentary disturbance of the forearms and legs.

Incontinentia Pigmenti Presented by DR MARION SULZBERGER and DR DAVID BLOOM

J. M., a girl aged 1 year, presents an eruption on the trunk and lower extremities which was noticed shortly after her birth. The past history and the family history are essentially irrelevant. The eruption is most pronounced on the sides and the anterior aspects of the trunk. It consists of gray-brownish pigmented streaks arranged in wavy parallel lines or in the form of a network. On the left flank there is a small, irregularly shaped, darkly pigmented nevus and a linear verrucous nevus on the back of the right hand. The scleras show a bluish tinge, which was also noticed in the mother.

DISCUSSION

DR CHARLES WOLF: I did not know about the hereditary aspect in the Chinese child. In the white child there are recessive characteristics.

DR HENRY SILVER: What is the relationship of the nevus to incontinentia pigmenti?

DR DAVID BLOOM: In congenital diseases one often finds associated other congenital defects. It is not surprising, therefore, that one sees in our case also verrucous nevus on the hand and nevus flammeus on the arm. There are also bluish scleras, which are likewise seen in the mother. It is, I feel, an unusual experience to see 2 such cases at one meeting. The cases which I have encountered involved adults in whom there was only a small number of pigmented lesions. It is probable that these lesions gradually diminish in extent. Therefore, such an extensive eruption is not seen in adults. The systematic arrangement of these pigmented lesions resembling a systematized nevus is also remarkable. Some authors are of the opinion that such a systematic arrangement of this pigmentation does not occur. The diagnosis of incontinentia pigmenti is made from the bizarre-shaped pigmented lesions and from the color, which is peculiarly grayish blue and which is explained by the pigment dropping down from the epidermis into the corium. Microscopically, one ought to see more chromatophores in the corium which are not melanoblasts and therefore should give a negative dopa reaction. This condition is a minor ectodermal defect and follows a dominant mode of inheritance and is frequently associated with defects of teeth, nails and hair. It has been observed that the cases may be associated with serious conditions, as in the case of Sulzberger and that of Naegeli. Reference is made to glioma of the eye, microcephaly and other serious states. It is advisable to have the children examined thoroughly.

Familial Benign Chronic Pemphigus (Hailey and Hailey) Presented by DR NATHAN SOBEL and DR JULIUS J. POLLOCK

A Case for Diagnosis (Allergic Dermatitis? Chronic Discoid Lichenoid Dermatitis?) Presented by DR HARRY B. FEILER

Eczematous Contact Dermatitis Following Preparation of Penicillin Solutions Presented by DR HENRY SILVER

Erythema Annulare Centrifugum (Mycosis Fungoides?) Presented by DR CHARLES WOLF

BROOKLYN DERMATOLOGICAL SOCIETY

David M Davidson, M D, *President*

Seymour H Silvers, M D, *Secretary*

May 20, 1946

A Case for Diagnosis (Leprosy?) Presented by DR C THOMAS CHIARAMONTE

A Case for Diagnosis (Periphlebitis Nodularis, Necrotizing?) Presented by DR C THOMAS CHIARAMONTE

Rosacea-Like Tuberculid of the Face Presented by DR LESSER M FRUCHTBAUM

Argyria Presented by DR DAVID M DAVIDSON

Chronic Discoid Lupus Erythematosus Presented by DR LESSER M FRUCHTBAUM

Abraham Walzer, M D, *President*

Seymour H Silvers, M D, *Secretary*

Jan 20, 1947

Disseminated Subacute Lupus Erythematosus Presented by DR SEYMOUR H SILVERS

Lymphogranuloma Venereum Presented by DR LOUIS J FRANK

Perifolliculitis Capitis Abscedens et Suffodiens Presented by DR N M. ESTRIN

C K., a Negro aged 24, was admitted to Kings County Hospital in October 1946 with a diagnosis of acute rheumatic fever and a pustular infection of the scalp Six months before, pustular lesions first developed on the scalp and buttocks, which were incised and treated with hot, wet applications of boric acid. These lesions continued to drain and extend to the entire scalp.

On his admission to the hospital, the entire scalp was covered with a red, crusted and bloody mass. Marble-sized pustules could be seen and felt underneath the crust. Treatment consisted of applications of wet dressings of isotonic sodium chloride solution, and epilating dose of roentgen rays, 100,000 units of penicillin parenterally every three hours for ten days and furacin®-soluble dressing.

At present there is no hair on the scalp which shows irregular areas of atrophy and scarring.

DISCUSSION

DR DAVID M. DAVIDSON I want to compliment the presenter on the results obtained in a difficult case

A Case for Diagnosis (Lichen Nitidus?) Presented by DR LOUIS J. FRANK

A Case for Diagnosis (Lymphoblastoma? Sarcoidosis?) Presented by
DR SEYMOUR H. SILVERS

Healed Gumma of the Anterior Chest Wall Presented by DR C. B. LOCASIO

CHICAGO DERMATOLOGICAL SOCIETY

Marcus R. Caro, M.D., *President*

Leonard F. Weber, M.D., *Secretary*

March 20, 1946

Sarcoid Presented by DR. EDWARD A. OLIVER and (by invitation) DR. A. GRENARD

L. L., a Negro clerical worker aged 42, gives a history of having first noticed a nodule on the right cheek in September 1943 while at an Army station at Staten Island, N. Y. Similar nodules appeared, subsequently increasing in size and number. The lesions observed today about the face and mucous membrane of the mouth appeared in August 1944. He first complained of hoarseness six months ago. There have been no weight loss, night sweats, cough or weakness. All other systems are essentially normal. He had a tonsillectomy in February 1944 and a replacement of a left detached retina in July. The family history is noncontributory.

The presenting lesions are nodules, papules and infiltrating purplish plaques about the nostrils, both cheeks, eyes, ears, neck and upper part of the thorax. There are nodules in the mucous membranes of both lips. Indirect laryngoscopic examination revealed no abnormalities. The lesions are not anesthetic to light touch or to painful stimuli. There is regional lymphadenopathy. Direct laryngoscopy was refused by the patient.

The urine was normal. The Kahn reaction of the blood was negative. Complete blood cell counts revealed relative leukopenia, averaging about 5,500 leukocytes. The differential count was normal. Examination of the chemical content of the blood showed normal urea nitrogen, sugar, calcium and phosphorus. Total proteins were 8.4, albumin 6.0, globulin 2.4, alkaline phosphatase 10.0 and acid phosphatase 37 mg. Smears from the nose and from a lesion on the face revealed no lepra bacilli. The roentgenographic examination of the chest showed bilateral hilar adenopathy consistent with sarcoidosis, while that of the metacarpal bones showed some suggestion of cystic changes.

Sarcoidosis? Presented by DR. CLEVELAND J. WHITE and (by invitation) DR. ROBERT C. RANQUIST and DR. KENNETH C. BAKER

A. C., a white woman aged 66, first noticed a lesion on the ala of the left nostril in January 1944. Gradually new ones appeared on the left cheek and left side of the forehead above the eyebrow and on the right side of the chest and middle part of the back. Some itching was present. In the last six weeks she has had the lesions treated with solid carbon dioxide except for the one on the chest, which was used as a control patch. There has been some improvement in all the lesions so treated, less elevation, less marginal activity and central clearing. The Kahn reaction of the blood was negative. The urine and blood were normal.

Histologic examination revealed sharply circumscribed nodules in the upper middle part of the corium which were separated from one another by connective

tissue septums, composed almost solely of epithelioid cells. There was a moderate lymphocytic infiltration around the cutaneous appendages and a dilatation of the capillary loops of the papillae. The epidermis overlying the nodules in the corium showed flattening and obliteration of the interpapillary prolongations.

Boeck's Sarcoid Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR M S KAGEN

L H, a 32 year old Negro, noticed a nodule on the left ala of the nose six months ago. A slight amount of white material was expressed from the lesion by squeezing. The lesion did not ulcerate. It gradually extended to involve the septum, being about $\frac{1}{2}$ by $\frac{1}{4}$ inch (1.3 by 0.65 cm) in size.

In 1939, an enlargement of the inguinal lymph nodes developed, which has persisted. In May 1944, two penile lesions appeared, for which the patient received eight weekly injections. At the present time generalized adenopathy is present. There are no systemic symptoms, the patient sought medical aid only for relief of the lesion on the nose.

The Kahn reaction of the blood was negative. The examination of the blood showed 75 per cent hemoglobin and 3,200 leukocytes. The urine was normal. A roentgenogram of the chest revealed a widening of the superior mediastinal region which may be compatible with a substernal goiter or mediastinal tumor. A roentgenogram of the hands showed no abnormality.

DISCUSSION

DR HENRY E MICHELSON, Minneapolis: There is little new that I can state about sarcoid, but I would like to call attention to the fact that the microscopic observations of sarcoid are not so clearcut as has been formerly thought. I am sure that there is considerable variation in the picture and that necrosis may occur. The more I see of sarcoid, the more I realize the necessity of complete general examinations by a group interested in the involvement of special organs.

DR RUBEN NOMLAND, Iowa City: I believe that one of the patients did not show changes in the blood proteins. There was a decided elevation of the serum albumin. According to statements in the literature the serum globulin is usually elevated and the serum albumin is usually normal. I think that every patient with sarcoid should have the serum proteins determined, but I do not believe that the observations of alteration in the serum proteins are consistent or of diagnostic importance.

DR FRANCIS E SENEAR: Dr Cornbleet called my attention last week to an article by Sezary in the *Presse medicale* in which he emphasized that we have to revise our concept of sarcoid, as our present day concept of the histologic aspects of this disease is too limited and that many cases of sarcoid will be overlooked if we insist on too characteristic a pathologic picture.

A Case for Diagnosis (Solid Edema?) Presented (by invitation) by CAPTAIN GROVER C DILS, Chicago

E A H, a boy aged 18, stated that in February 1945 he had an infected nail of the first toe of the right foot and septicemia of the right foot and leg developed. He recovered with sulfonamide drug therapy, but two weeks later swelling of the left cheek developed, which was painless and caused no discomfort.

but did not clear up. During the summer of 1945, the heat and sweating caused the left cheek to swell more and become erythematous and papules began to develop in this area. The papules became pustular, but only briefly so. The process then spread to the bridge of the nose and across to the opposite cheek. It also began to involve the left eye in a periorbital edema and conjunctivitis. He took four roentgen ray treatments in the fall of 1945 with temporary improvement but was inducted into the Army in November. He then became much worse, with involvement of the right eye and a much greater swelling and erythema of both cheeks. There is no pain and only occasional itching.

While the patient was at Gardiner Hospital various examinations were carried out for foci of infection, but none were found. He has been treated with aluminum subacetate cool packs and lotia alba, a low fat diet, and, finally, on February 27, roentgen ray therapy was started. He seems to improve spontaneously, and flare-ups occur the same way.

Physical examination reveals erythematous indurated skin over both cheeks with small flat papules and an occasional pustule. There is thickening of the skin over the bridge of the nose. The hair follicles on both cheeks are greatly dilated. The blood pressure was 104 systolic and 72 diastolic.

The roentgenographic examination of the sinuses and chest showed no abnormalities. The Kahn reaction of the blood was negative. The sedimentation rate on March 18 was 15 mm. The most recent examination showed the urine to be normal. The blood was normal.

A Case for Diagnosis (Solid Edema?) Presented by DR FRANCIS E SENEAR

This patient, A. R., was originally seen on March 19, 1942, by Dr. Edward A. Oliver, who stated that he had fairly severe acne rosacea accompanied with considerable seborrhea of the scalp. In addition, he had a large edematous swelling of the forehead in the glabellar region, this being suggestive of persistent edema. He was not seen again until one year later, at which time he complained that the edema in the glabellar region, which had been present since his visit in 1942, had become much more pronounced in the last four months.

The patient has been seen intermittently from February 1945 until the present time. Throughout this time he has had exacerbations of rosacea, and he has had persistent edema occurring in a triangular outline in the glabellar region. The left upper eyelid eventually began to be involved in the edematous process, and during the past few weeks the right upper lid has also become involved. The patient has had intensive penicillin therapy, and the edema has shown improvement. After this the length of the sides of the triangle reduced from 7.5 cm to 5.5 cm. The involvement of the right upper lid, however, has developed subsequent to the use of penicillin, which was given early in December.

A Case for Diagnosis (Solid Edema Following Repeated Attacks of Streptococcic Dermatitis?) Presented by DR FRANCIS E SENFAR

Since 1937, this patient, W. C., has had an eczematoid eruption involving the external ears, this being at most times of impetiginous character. He was seen several times from 1937 to 1939 with recurrent attacks. In September 1945, he stated that eventually he began to have acute inflammatory attacks in which the ears became swollen, at first at about intervals of about a year and later at intervals of about six months. He had two attacks in September. When seen on this occasion he presented a picture of solid edema on each external ear, worse

on the left side Roentgen ray therapy was used, and he has had an intensive course of penicillin therapy The latest acute attack of erysipelatos type occurred on January 24

DISCUSSION

DR ADOLPH ROSTENBERG JR (by invitation) It seems to me that these cases present two problems One is restitution, if possible, of the damage that has already occurred, namely, the fibrosis, which might be amenable to injections of boiling water The other is to see whether further damage can be prevented I cannot present any particular solution to the latter approach I do not believe that the fact that treatment may have failed in any given case means too much The difficulty is finding to what the patient is sensitive It seems to me that such an entity as this must have multiple possibilities as to the sensitivity, and ultimately by virtue of repeated lesions changes may develop which are not reversible

DR STEPHEN ROTHMAN In the second case of Dr Senear I would like to suggest the diagnosis of recurrent erysipelas It is rather common for erysipelas to recur every few months over a period of many years when there is a rhagad or erosion between the toes, in the nares or in the external auditory canal Because of the recurring attacks, solid edema develops By finding and eliminating these portals of entry, my co-workers and I have prevented further recurrences in all our cases and the solid edema has regressed considerably in most of them It does not make any difference whether the cracks are caused by fungous infection, by bacterial infection, by simple maceration due to hyperhidrosis or by chronic scratching A few days ago I saw a woman with recurrent erysipelas and lymph stasis of the face She had seborrheic dermatitis of the scalp with a crusty spot at the hair line, which she admittedly had been scratching violently I cannot understand the theory that the recurring febrile attacks with reddening and swelling of the legs represent dermatophytids How can one explain the prompt response of the acute attack to sulfonamide drugs or penicillin? How can one explain the cases in which there are no fungi present and what the mechanism of the lymphedema is?

DR FRANCIS W LYNCH, St Paul I think that something is lost when cases such as these are grouped for discussion Though there are clinical resemblances, I think that it is important to point out the dissimilarities, some patients present chiefly edema, others fibrosis and others more inflammation, and in many cases there is a mixture of two or three of these features Perhaps the chief concern should be the determination of the source of the inflammatory reaction in the particular case Some conditions are preceded by a superficial chronic dermatitis which might be infectious in nature The area of dermatitis could be the portal of entry for deeper infection, as is the case when fissures are present, as Dr Rothman pointed out As Dr Oliver pointed out there are cases in which the persistent edema is the chief feature, and those cases are amenable to the treatment he outlined

DR HERBERT RATTNER As I understand it, no source of infection was found in the first of the 3 cases I should like to ask whether it is of advantage to give such a patient Dr New's treatment while the solid edema is still in the process of development, or should one wait?

DR ADOLPH ROSTENBERG JR The focus of infection theory seems to fit in with what Dr Rothman calls recurrent erysipelas In a given number of these cases, one finds a given number with infection In any number of cases of seborrhea of the scalp portals of entry will be found, but solid edema does not develop There is something different in these patients that causes the solid edema

DR STEPHEN ROTHMAN My remarks were concerned with the portal of infection for recurring erysipelas and development of solid edema. This has nothing to do with the theory of distant foci.

DR FRANCIS E. SENEAR I think that you are all talking about the same thing. To me solid edema is an end result. I am thoroughly in accord with Dr. Rothman as to the picture in the ear. That is why I labeled it repeated attacks of streptococcic dermatitis. Whether one calls it that or recurrent erysipelas is not important. The point is that one does see patients who have repeated attacks of dermatitis such as he has, the more recent of which was illustrated in the kodachrome® slides. One sees other patients who do not have this history of acute recurrent attacks, but where does this eventually develop? I agree with Dr. Lynch, depending on the stage at which one sees the patient, there may be either fibrosis or true edema. I showed this patient with the glabellar involvement because I never saw a case of solid edema like this before. Both of these patients have been examined repeatedly by competent nose and throat specialists and internists. I have seen such conditions repeatedly and have never been able to find portals of entry.

Psoriasis Arthropathica Presented by DR STEPHEN ROTHMAN and (by invitation) DR Z. FELSHER

DR STEPHEN ROTHMAN The most satisfactory explanation for the association of arthropathy and psoriasis was given by Julius Bauer. In his genetic studies he found families in which single members suffered from psoriasis, others from arthritis and others from arthropathic psoriasis. Apparently there is a defect of conjugated genes.

Pemphigus Erythematosus (Senear-Usher Type) Presented by DR S. J. ZAKON

S. S., a Jewish man aged 27, stated that his eruption developed in September 1943, while he was stationed in San Marcus, Texas. The eruption appeared first on the chest and was at first considered to be impetigo. This eruption soon spread to the back, abdomen, extremities and finally to the face. At no time did he have sores in the mouth. He was hospitalized and received courses of sulfonamide preparations, germanin (a German dye substance derived from naphthalamine sulfonic acid), penicillin, vitamins, roentgen rays and ultraviolet irradiation. In April 1944, he contracted a secondary infection of the skin and was febrile for some time. After his recovery from the febrile episode the skin showed considerable improvement. From June to August he was at Hines Hospital, where he received courses of acetarsone (3-acetylamino-4-hydroxyphenyl-1-arsonic acid) and large doses of vitamin D.

Examination shows on the forehead a number of discrete reddish brown, slightly elevated papules with adherent scales, and on the face brownish red patches on the flush areas involving both lower eyelids. On the cheeks and neck there are discrete brownish red papules and patches. On the chest, back and abdomen there are a large number of lesions in various phases of evolution and/or involution. Fresh bullae are not seen. The Nikolsky sign is absent. A few areas are denuded but most of the lesions show either a grayish scale or thick keratotic scale crusts. The mucous membranes show no involvement. The results of the general physical examination were good.

DISCUSSION

DR EDWARD A OLIVER I have seen and watched this patient for the past three years. He is said to have had pemphigus vulgaris in the Army. I first saw him at the Veteran's Hospital where he presented about the same picture that he shows today, except that when I first saw him he had no lesions on the face. I have never seen any bullae on the skin—the commonest lesion is a fairly large oval papular lesion covered with an adherent crust. When he was first seen, the diagnosis of pemphigus erythematosus was made and he was given acetarsone. In addition, he was given vitamin D, 100,000 units three times a day. He has not become any worse, nor is he any better, despite all this treatment.

I have another patient who is getting the same treatment, and I can see little improvement in her condition after a year of this therapy. I have, however, seen this treatment work wonders temporarily in 2 cases of severe pemphigus vulgaris.

DR FRANCIS E SENFAR It was interesting to see the reversal in the direction of the clinical picture in this case. I have seen several patients who have started out with a pemphigus-erythematosus picture, and then the picture has changed and become one of typical pemphigus vulgaris with rapid death. This is the first one I have seen in which there was a history of onset with pemphigus vulgaris.

DR MAURICE OPPENHEIM (by invitation) I asked the patient where his pemphigus started. It started on the chest three months before he got the general eruption. As in many cases of pemphigus vulgaris a primary lesion precedes the general rash. I believe, also, that the Seneear-Usher syndrome is a kind of primary lesion of pemphigus located on the face. The diagnosis of pemphigus can be made only on the basis of the course of the disease. One cannot make the diagnosis from few lesions. I stressed repeatedly that the treatment with acetarsone should start when the primary lesion is present. Impetigo on the predilection areas which does not heal is likely to become pemphigus.

With respect to the treatment with acetarsone, such treatment must be made in the right way. I found that it was possible to change the clinical course of pemphigus so that nodules and papules would develop instead of blisters and blebs. Kromayer said, after using my treatment, that he was able with acetarsone to change the clinical aspect of pemphigus. Therefore, it is difficult now to make a diagnosis of pemphigus in this case after the use of acetarsone.

My method of treatment with acetarsone must be followed strictly, as I pointed out in my paper, "Acetarsone in the Treatment of Pemphigus" (*ARCH DERMAT & SYPH* 47 40-42 [Jan] 1943), in collaboration with Dr D Cohen. In some cases I give up to 600 tablets (150 Gm) over a period of several years. The intermission is important for the elimination of acetarsone.

DR R H SCULL In the case of pemphigus foliaceus I presented at the Mississippi Valley Conference I have been using the treatment suggested by Dr Oppenheim. Now the patient has the same lesions of pemphigus erythematosus that this patient has, although the treatment with stovarsol is the same, the lesions are not improving.

Linear Nevus Presented by DR CLEVELAND J WHITE

A Case for Diagnosis (Atrophy of the Scalp) Presented by DR FRANCIS E SENEAR and DR MARCUS R CARO

A R, a white man aged 51, was seen in the Department of Dermatology, University of Illinois Research and Educational Hospital, with the complaint of

localized loss of hair, at the site of a scalp injury sustained eighteen months previously. There were complete alopecia and considerable atrophy of the skin, in an irregularly oval area at the vertex. At the periphery of the bald patch, perifollicular inflammation and pustulation were present. Irregular pseudopodial projections of the process into the surrounding scalp were noted.

A biopsy specimen taken from the active border of the patch showed intracellular and intercellular edema of the epidermis. In the upper part of the corium, the blood vessels were dilated and there was diffuse edema. Deeper in the corium there were large poorly defined inflammatory areas. These contained densely packed lymphocytes, connective tissue cells and fibroblasts and included areas of necrosis. About these inflammatory areas there was considerable fibrosis.

DISCUSSION

DR. CARL W. LAYMON (Minneapolis): The question of scarring alopecia is a source of confusion to most dermatologists. Recently I have been interested in folliculitis decalvans and pseudopelade and have tried to get a few cases to study histologically. A few points regarding these diseases may be mentioned. First, it makes a tremendous difference as to the location from which the biopsy specimen is taken. If one takes a biopsy specimen from the central part of a plaque of lupus erythematosus, pseudopelade or folliculitis decalvans, the changes are almost identical in all. It is almost impossible to make a differentiation between these various conditions in an old lesion. If one takes the specimen from an early lesion and at the border, there are sometimes signs that permit one to make a differentiation.

It is difficult to study enough cases of cicatrizing alopecia because they are so rare. Except in sections containing a pustule in folliculitis decalvans, the changes look like those in pseudopelade. In lupus erythematosus of the scalp the infiltrate is usually heavier and more diffuse than in pseudopelade or folliculitis decalvans.

DR. FRANCIS E. SENEAR: Are there any impressions as to what the diagnosis really is?

DR. MARCUS R. CAPO: We have no definite diagnosis to offer. When we first saw the patient there was folliculitis about the edge of the atrophic patch and a tentative diagnosis of folliculitis decalvans was made. After treatment with penicillin ointment the folliculitis disappeared and the picture developed that is seen today. Histologically there is no folliculitis, but the section shows inflammatory areas that extend deeply into the corium. All we can say is that apparently there is an infection here, but at present no active folliculitis decalvans.

Pityriasis Rubra Pilaris. Presented (by invitation) by Dr. H. H. ROBIN.

A Case for Diagnosis (Lichen Urticatus?). Presented by Dr. CLEVELAND J. WHITE and (by invitation) Dr. ROBERT C. RANQUIST and Dr. KENNETH C. BARTO.

R. C., a white girl aged 3 has had an eruption on the face, arms and legs since June or July 1945. There have been numerous remissions and exacerbations. Numerous local applications have been used without avail. Orange juice has been replaced by ascorbic acid and tablets. In recent weeks, all chocolate products have been eliminated and all the food has been cooked.

The urine was normal. The examination of the blood showed 4,869,000 erythrocytes and 10,260 leukocytes with 71 per cent polymorphonuclear leukocytes,

26 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 97.4 per cent hemoglobin

DISCUSSION

DR STEPHEN ROTHMAN Lichen urticatus is well defined morphologically as an itching disseminated eruption consisting of lesions with an urticarial base and a papule or vesicle on top. In all my cases elimination of eggs from the diet has led to rapid recovery, and I believe that in most, if not in all, cases the eruption is due to sensitivity to egg white.

DR ADOLPH ROSTENBERG JR (by invitation) I am interested in Dr Rothman's remarks on sensitivity. Most of us believe that there should be some sensitivity in these cases. I do not believe that anyone has shown any concrete evidence. A number of years ago Walzer in Brooklyn studied cases of lichen urticatus and came to the conclusion that no causal food or inhalant allergic background could be demonstrated. When I was at the New York University-Bellevue Medical Center Dr Sulzberger and I studied these cases but could not find any allergic background. I have not tried Dr Rothman's suggestion, but I will try it. In Washington we used to see many of these cases. Dr Harry Anderson pointed out that most of the children ate too much of carbohydrates, particularly "pop." It might be interesting to study the sugar tolerance to see what it is in these patients.

DR THEODORE CORNBLEET We have been able to corroborate the experience of the English that the disease in hospitalized children clears up spontaneously. Their lichen urticatus eruptions reappear promptly, however, when they go home. Of course, these children eat eggs while in the hospital. Dust has been suspected by some.

DR HERBERT RATTNER I have seen 3 cases at the Michael Reese Hospital which apparently were due to the ingestion of chocolate. There was improvement when all chocolate was eliminated and recurrence when it was again ingested.

DR FRANCIS E SENEAR Why is it, if this is due to sensitivity, that most of the patients are so much worse in the summer and better in the winter? Secondly, if the condition is due to sensitivity, why is it almost always confined to dispensary practice? I should think that the possibility of sensitivity to egg would be greater in children of private patients than in dispensary patients.

DR MINNIE O PERLSTEIN There have been a number of instances in which children seen at 2 or 3 years of age with lichen urticatus have at a later age had true atopic dermatitis, either as such or as part of a generalized clinical allergic manifestation.

DR STEPHEN ROTHMAN I did not carry out cutaneous tests with egg white solution, and my observations have been purely clinical. Elimination diet terminated the eruption promptly in cases in which the disease had been present for many months.

DR ROBERT L BARTON (by invitation) I would like to know whether anyone has tried diphenhydramine hydrochloride (benadryl hydrochloride®) in lichen urticatus.

DR JAMES H MITCHELL I used benadryl®, ½ capsule (25 mg), in a small boy, and he slept for two or three days.

DR SAMUEL ZAKON I believe that if the benadryl® were given to the mother whose child had lichen urticatus it might be helpful. I believe that it is the neurotic mothers that are the contributory cause in lichen urticatus. I tell the mothers to read Dr Aldrich's book, "Babies Are Human Beings." I usually give phenobarbital

to the mother, and my results are as good as those of Dr Rothman, who treats his patients with elimination diets

A Case for Diagnosis (Lichen Scrofulosorum?) Presented by DR FRANCIS E SENEAR and (by invitation) DR P BOSWELL.

C J, a Negro infant aged 14 months, was referred from the Department of Pediatrics, University of Illinois Research and Educational Hospital. There was a history of a slightly pruritic eruption of five weeks' duration and of swelling of the right middle finger for about the same length of time. General physical examination revealed nothing of significance except a tense, fusiform, only slightly tender swelling of the middle finger of the right hand. The result of a Mantoux test was strongly positive, all other laboratory studies, including the serologic test for syphilis, elicited negative reactions. Roentgenographic examination of the affected finger showed an expansion of the shaft of the proximal phalanx with some irregularity of the bone structure, suggestive of spina ventosa.

Dermatologic examination showed a generalized eruption, consisting of discrete papules, generally skin colored, up to pinhead size, in places surmounted by a fine scale. A few of the lesions were excoriated. Histologic examination of a specimen from the back showed a normal epidermis. There was a slight lymphocytic infiltrate about the duct of the sweat gland and about the superficial blood vessels.

DISCUSSION

DR MAURICE OPPENHEIM (by invitation) I think that the disease is prurigo mitis of Hebra. It is a very common disease in Vienna. There are two kinds of prurigo mitis of Hebra. In one the eruption appears on the extensor aspects of the legs and arms and consists of equal-sized hard nodules, better felt than seen, with a high degree of itching. The lymphatic nodes in the femoral and inguinal areas are enlarged and indurated. This syndrome is characteristic for prurigo mitis. I consider prurigo mitis as a vitamin D deficiency. Before vitamin D was known, Hebra and Kaposi treated such patients with cod liver oil and they improved. Now they are treated with ultraviolet rays and vitamin D with the same result. Often prurigo of Hebra is connected with rickets. I would like to ask Dr Senear whether he treated the child with vitamin D. This disease is extremely rare in the United States. The presented histologic picture is typical for prurigo of Hebra.

DR FELIX PINKUS (by invitation) I must apologize to Dr Oppenheim for a very different thought in this case. I saw such a case in an adult, I saw it in a Negro, and I saw it in the same form as in this case in the Receiving Hospital. There was an eruption about the same as you saw in this patient, but it was on the arms, and my co-workers and I could not make a diagnosis on microscopic examination. There was a follicle not like a tubercle, but something near to a tuberculid. There were vesicles on the side with some giant cells, and in the center there was necrosis. It is a form of tuberculid. Examining the section microscopically before I saw the patient, I took it for a tuberculid. When I saw the patient the eruption was quite the same as in this child today. It could be lichen scrofulosorum, but I do not think that it is. As near as I can judge these 2 cases, this one today and the one I saw in the adult, the disease is the same. It is not the well known form of tuberculid as seen in Negroes. I have never seen it in this form in the white race, and I have seen many cases of tuberculid in white patients. After seeing other cases I came to the conclusion that it must be a

tuberculid, with tuberculosis in the other organs. After seeing the same form in this child today, it looks like a certain form of tuberculid without a name.

DR M J REUTER, Milwaukee. The clue to the cutaneous diagnosis is the spindle-shaped dactylitis on the right index finger. That could be either syphilis or tuberculosis. I did not see the roentgenogram of the finger, but, in view of the positive reaction to the tuberculin test, I believe that this is a follicular papular tuberculosis, namely, lichen scrofulosorum.

DR R H SCULL. The Negro skin will show these minute papular and ketatotic lesions from the mildest amount of toxicity due to many causes. When lichen scrofulosorum has been suspected, at no time has a histologic picture corresponded to that described in standard histopathologic textbooks. I was glad to hear Dr Pincus' discussion.

DR MAURICE OPPENHEIM. I do not agree with Dr Pincus. In spite of the fact that the child has tuberculosis, I believe that my diagnosis is correct. The mother told me that the child has intense itching. A tuberculid does not itch. In the histologic picture I did not see epithelioid or giant cells. I believe that this is a case of prurigo mitis of Hebra, which is almost unknown in America. In lichen scrofulosorum there is grouping, but not in prurigo. This case is typical for the classic description of Hebra and of others of prurigo mitis.

DR RUBEN NOMLAND, Iowa City. I agree with Dr Scull about the tendency of the Negro skin to produce lichenoid papules in different circumstances. I believe that a number of things can produce such an eruption. One would assume that this is probably lichen scrofulosorum caused by a tuberculid reaction.

DR FRANCIS E SENLAR. I appreciate Dr Oppenheim's diagnosis, because when I saw this patient I commented with respect to the lesions on the arms, that clinically they were exactly like the lesions of lichen scrofulosorum. Strophulus is a term that has been used in several ways. To me it is the same as lichen urticatus. Dr Oppenheim pointed out that there was no grouping, but in lichen scrofulosorum early in the course there is no grouping, it is only later that the lesions become grouped. Third, the textbooks describe a papulovesicular type of lesion occurring in lichen scrofulosorum which is different from the ordinary type.

With regard to itching, this as a rule does not occur in tuberculosis, but I have known Negroes to itch from many things that do not cause trouble in the white person. Workers at the Intensive Treatment Center say that many of the Negro patients with early syphilis complain of pruritus. As Dr Oppenheim pointed out, prurigo is not seen in either the mitis or the ferox variety. I recall a year ago when I showed a patient, Dr Oppenheim said that the disease was typical of prurigo and Dr Rothman, who also has had experience with this disease abroad, said that it was not.

I do wish to emphasize, as did Dr Scull and Dr Nomland, that the Negro skin has different manifestations. I do not believe that one can depend on the clinical course of the disease and the tendency of lichen scrofulosorum to disappear. From the roentgenogram of the fingers the diagnosis was spina ventosa.

Discoid Lupus Erythematosus Presented by DR FRANCIS E SENLAR and DR MARCUS R CARO

An 8 year old white boy was admitted to the Illinois Research and Educational Hospital on Feb 16, 1946, with a dermatosis of seven months' duration. The eruption, which was limited to the face, appeared soon after exposure to intense sunlight and had since repeatedly flared after similar exposures. There were no

associated constitutional symptoms. The past and family histories were non-contributory. There had, however, been frequent contact with a family friend who was known to have tuberculosis. In addition, a history was elicited of cold allergy with urticarial manifestations. The general physical examination revealed no abnormalities. The sedimentation rate, hemoglobin and erythrocyte count were within normal limits, the leukocyte count was 4,400 per cubic millimeter. A sternal puncture showed normal bone marrow. Roentgenographic examination of the chest showed accentuation of the hilar and bronchovascular markings. The result of a tuberculin patch test was moderately positive.

Dermatologic examination revealed an eruption on the face limited to the "butterfly area." The skin in this region was erythematous and showed some plugging of patulous follicles and, in places, a thin adherent scale.

During the patient's hospital stay there was almost complete regression of the eruption. Biopsy was not performed.

Lupus Erythematosus, Subacute Disseminated. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. A. L. SHAPIRO

F. L., a white woman aged 61, first noted the appearance of pruritic erythematous spots on the left preauricular area and dorsum of the left hand in August 1945. These cutaneous manifestations were preceded by several months of irritability and fatigue. During the ensuing months the cutaneous lesions spread to other areas and increased in size. In addition, the patient lost 10 pounds (4.5 Kg.) in weight.

On Feb. 28, 1946, the patient was admitted to the University of Chicago Clinics. She presented large scaling and crusted plaques on both cheeks and a number of similar small and large erythematous lesions with eroded arciform borders on the fingers, hands, forearms and chest. Bluish white patches with erythematous halos were noted on the buccal mucous membrane across the dental closure line bilaterally.

The leukocyte count was 4,900, and the differential count revealed 36 per cent polymorphonuclear leukocytes and 56 per cent lymphocytes. The remainder of the blood cell count as well as the urine, blood lipids, nonprotein nitrogen and plasma proteins were normal. The sedimentation rate was 26 mm. per hour, and the urea clearance test showed slightly reduced function. The serologic reaction of the blood for syphilis was negative.

Within a period of three days the patient was given 20,000,000 units of penicillin intramuscularly (1,000,000 every three hours). This treatment had to be interrupted because of severe chill, fever and fainting spell.

Histologic sections from the skin and buccal mucous membrane are presented and show the characteristics of lupus erythematosus.

DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul. It is interesting to observe lupus erythematosus in childhood because it stimulates new lines of thought. Not long ago Stokes and his associates pointed out the numerous factors which influenced the course of lupus erythematosus. It is unlikely that certain of these factors are of importance in children, for example the hormonal factors and certain of the infectious factors. I think that this child has discoid lupus erythematosus; it is interesting to note the roentgenologic changes in the chest. Roentgenologists are increasingly concerned with the changes found in lupus erythematosus, and at least some of them think that they are somewhat specific so that one can at least suggest the clinical diagnosis of lupus erythematosus after roentgenologic study of the chest.

I agree with the diagnosis in the case of the older woman, though I think it uncommon to see the active stage of lupus erythematosus at her advanced age. The sharpness of the border is the striking feature of her eruption.

DR EDWARD A. OLIVER: I was interested in seeing the improvement in Dr Rothman's case. I saw this patient three weeks ago with Dr Rattner, and we, too, made the diagnosis of subacute lupus erythematosus. She certainly has responded well to treatment. When I first saw her, the lesions were inflammatory and the borders were dike-like elevations. Because of the symmetry of the lesions, the fact that the patient was febrile and the feeling of general malaise, I felt that she was suffering with subacute lupus erythematosus.

DR HERBERT RATTNER: I think, as Dr Oliver does, that the improvement can be credited to the penicillin rather than rest in bed. The clinical picture in this case was indeed unusual.

DR M. J. REUTER, Milwaukee: I believe that it was at the last meeting that Dr Rothman mentioned improvement clinically in a patient with acute lupus erythematosus, from penicillin in doses comparable to those given in subacute bacterial endocarditis. For the last three weeks I have been giving a woman with acute lupus erythematosus 500,000 units a day. She is rapidly getting worse despite this therapy.

DR EARLE PACE: Relative to the age, I had the unfortunate experience since last summer of seeing 2 patients with the disease in an acute stage, women of ages 68 and 71. The disease started after sunburn last summer. Both are dead.

DR MARCUS R. CARO: The child has done remarkably well after rest in bed. The lesions have nearly disappeared with bed rest and a diet high in vitamins.

DR STEPHEN ROTHMAN: I agree with Dr Lynch and Dr Oliver that this was an odd eruption. I was much relieved when I heard that Dr Oliver had diagnosed it lupus erythematosus, and I admired his readiness to do so. Biopsy and laboratory examination have proved beyond doubt that this was lupus erythematosus. It is unusual to see eroded arciform edges. I agree that this patient did well with large doses of penicillin. Her rapid improvement can hardly be interpreted as due to bed rest or as being a spontaneous remission. My patient with acute lupus erythematosus whom I mentioned in the February meeting, who obtained a total of 76,400,000 units of penicillin in eight days, lived for six more weeks but died two days ago. The patient had verrucous endocarditis, but on histologic examination a striking feature was the scarcity of inflammatory cells in the vicinity of the lesions. No signs of penicillin damage were found at autopsy.

Vitiligo Presented by DR CLEVELAND WHITE and (by invitation) DR R. C. RANQUIST and DR K. M. BAKER

Keloid of the Scalp Present at Birth Presented by DR JAMES R. WEBSTER and (by invitation) DR FRANCIS HETREED

E. H., a white boy aged 9, has a lesion on the scalp which was present at birth and has not changed since that time other than to enlarge slightly; it is not growing proportionately to the growth of the child.

The patient is the sixth child in the family. There were no unusual events during the pregnancy. The delivery was normal, without instruments, after labor of only a few hours, and there is no history of appreciable caput succedaneum at birth. The mother has an interesting story to account for the lesion, according to common superstition.

The lesion is located in the midline of the scalp, approximately at the site of the posterior fontanelle. It is approximately the size of a 50 cent piece, well defined, ivory colored and irregularly stellate in shape, with a few pea-sized similar lesions at its periphery. The maximum elevation in the center of the lesion is about 4 mm. It is firm and moves easily with the scalp over the underlying bone. The surface is devoid of hair and is smooth and glistening. There is no roentgenographic evidence of underlying bony change.

The vaccination on the left arm, which according to the mother exhibited "a good take," has left only a smooth soft nonelevated pliable scar.

A survey of the literature fails to reveal reports of similar cases, and the patient is presented to ascertain whether any of the members have observed such a phenomenon.

DISCUSSION

DR MICHAEL H. EBERT: This is a case of permanent alopecia in a single area on the scalp which manifestly is not due to pseudopelade, lupus erythematosus, folliculitis decalvans or the usual causes of that type of alopecia. In addition, there is a large nodule which seems to be deeper than the corium, in fact, the skin can be moved over it. It seems to be in the hypoderm. The lesion has been present since birth. It is difficult to evaluate the possible result of trauma when the child was passing through the birth canal. According to the mother, there were no forceps used and no caput succedaneum occurred, nevertheless a minor trauma may have resulted in permanent scarring alopecia, as Dr. Finnerud showed in a series of cases he studied. There was no history in this case of a trauma which could produce a break in the surface of the skin or that could produce a keloid. It is true that keloid may follow trauma which does not break the surface. I am inclined to think that this is a fibrotic nevus.

DR MAURICE OPPENHEIM (by invitation): I agree with Dr. Ebert. This lesion belongs to the group of congenital aplasias. It is of nevroid type. It was first described by Voerner. The typical location is on the vertex. I have seen several cases of this kind, and many cases have been published. Sometimes it is a typical atrophy with absence of connective tissue, sometimes there is hypertrophy. It is no wonder that sometimes there is keloid formation. This disease belongs to the congenital circumscribed atrophy of the skin and is probably caused by amniotic concretion.

DR JAMES R. WEBSTER: I appreciate the discussion. It was my intention to perform a biopsy, but I thought that I would present the case first and then have the examination made.

In answer to Dr. Ebert, the lesion was present, as it is now, at birth and is not the result of trauma at delivery. It has the clinical picture of a hypertrophic scar. I do not know whether it is developmental and of the type Dr. Oppenheim suggests. One does see a substantial number of cases of spontaneous keloid occurring in grown persons with no antecedent trauma. I thought that this might be similar in character, but developing in intrauterine life.

Terebrating Basal Cell Epithelioma (Intermediate Cell Type). Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. Z. FELSHER.

Pyoderma Faciale (O'Leary) Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. A. S. SHAPIRO.

Generalized Progressive Scleroderma with Unusually Extended Ulcerations after Sympathectomy Presented by DR STEPHEN ROTHMAN and (by invitation) DR G F PINNE

Necrobiosis Lipoidica Diabeticorum in a Girl Aged 8 Years Presented by DR CLEVELAND J WHITE

DISCUSSION

DR HENRY E MICHELSON, Minneapolis When Dr Pinkus was with us, he went over our material on necrobiosis—we have had about 30 cases—and he brought out the fact that the microscopic observations were quite different in different patients We saw specimens that had decided necrobiosis and those that had considerable xanthoma in the slides and some that looked surprisingly like granuloma annulare The entire subject of the pathologic changes of necrobiosis could well be worked over, for there might be newer observations that could be added

DR MAURICE OPPENHEIM (by invitation) It is extremely rare to see the disease, which I described first, at this age There is always a diabetic history in these cases There was only 126 Gm of sugar in the blood in this case, but there is a diabetic history in other members of the family I do not believe that this disease exists without diabetes

Epidermolysis Bullosa, Acquired Type Presented by DR L F WEBER and DR IRENE NEUHAUSER

Hyperpituitarism Associated with Cutis Verticis Gyrata Presented by DR MICHAEL H EBERT and (by invitation) DR M S KAGEN

Tuberculosis Verrucosa Cutis Presented by DR MICHAEL H EBERT and (by invitation) DR M S KAGEN

A Case for Diagnosis (Lymphoblastoma?) Presented by DR THEODORE CORNBLEET and (by invitation) DR H SCHORR and DR M S KAGEN

Lepa, Lepromatous Type Presented by DR MICHAEL H EBERT and (by invitation) DR N L BAKER

Erythema on the Terminal Phalanges Two Cases Presented by DR THEODORE CORNBLEET and (by invitation) DR H SCHORR and DR M S KAGEN

Nevoxanthoendothelioma Presented by DR HERBERT RATTNER and (by invitation) DR H RODIN and DR N L BAKER

M B, a Negro girl aged 1 year, presents dark tumors on the body which appeared four months ago The mother was treated for syphilis during the time she was pregnant with this child Two Kahn reactions of the child's blood were negative

There are generalized soft painless pigmented round papules from 2 mm to 2 cm in size There is a large group of variable size on the abdomen, some of which are yellow in the center They are present in a linear arrangement on the posterior surface of the right leg

DISCUSSION

DR CARL W LAYMON, Minneapolis Nevoxanthoendothelioma is a rare disease This is the first time I have seen it in a Negro One of the features is the unusual number of lesions In McDonough's first case the lesions were limited in number There is usually no disturbance in the blood lipids and the lesions usually disappear spontaneously in six months to a year

DR MARCUS R CARO I had occasion to examine a section from this patient The section stained with hematoxylin and eosin was nearly identical with that in the case reported by Dr Senear and me some years ago (ARCH DERMAT & SYPH **34** 195, 1936) I agree with the diagnosis as presented

Fibrosarcoma. Presented by DR THEODORE CORNBLEET and (by invitation)
DR D COHEN and DR N L BAKER

Marcus R Caro, M D, *President*

Leonard F Weber, M D, *Secretary*

April 17, 1946

Generalized Herpes Zoster Presented by DR MICHAEL H EBERT and (by invitation) DR J GRAFFIN

A Case for Diagnosis (Pustular Eruption of the Palms and Soles). Presented by DR MICHAEL H EBERT and (by invitation) DR N L BAKER

J S, a white girl aged 17, first noticed an itching eruption on the palms and soles four months ago This did not improve with the usual soaks and ointments, but improved somewhat with sulfathiazole given by mouth There is a deep pustular scaling eruption on the insteps and on the thenar and hypothenar eminences of the hands The nails are stippled

DISCUSSION

DR CARL W LAYMON, Minneapolis This type of case presents a diagnostic and therapeutic problem I think that acrodermatitis continua or dermatitis repens could be ruled out in this case because of the symmetry Dr Ebert says there is no evidence of a fungous infection That suggests pustular psoriasis or pustular bacterid It is not difficult to make a diagnosis of pustular psoriasis if one sees actual psoriatic lesions on other parts of the body which, however, are not present here I favor a diagnosis of pustular bacterid, and it would be well to search for foci of infection if such has not been done

DR EDWARD A OLIVER I agree with the diagnosis of pustular bacterid I think as Dr Laymon does, that in the absence of any real signs of psoriasis, one must consider that diagnosis In pustular bacterid infections, the commonest locations are the thenar and hypothenar eminences of the palms and on the sides of the feet near the heels The lesions here are on the midportions of the feet, but if cultural examination for fungi is negative, I believe that the diagnosis of pustular bacterid must be considered The patient's teeth were in good condition, but I thought that one tonsil appeared enlarged and slightly ragged I am accustomed, in this type of case, to look carefully for a focus of infection, for only when that focus is removed does the condition clear up

DR STEPHEN ROTHMAN The patient has considerable hyperhidrosis, which is often associated with nonbacterial and nonmycotic dyshidrosis Although it is

true that the vesicles in dyshidrosis are not on top of sweat gland ducts, possibly the imbibition of the horny layer with sweat may be a factor in these vesicular eruptions which, as Dr Becker pointed out, are often associated with exudative neurodermatitis. Chemical analysis of the vesicle content will decide whether they originate from sweat. Emotional hyperhidrosis may well explain the assumed "functional" origin of dyshidrosis.

DR S W BECKER I think that this is the type of eruption that Tilbury-Fox called dyshidrosis. He said that these patients all have hyperhidrosis and that the lesions started as blocked-up accumulations of sweat. I do not believe that pustular psoriasis should be considered. I believe that the eruption which Andrews called pustular bacterid is simply pustular dyshidrosis, of which this is a classic example.

DR FRANCIS W LYNCH, St Paul My line of thought is much like that of Dr Rothman and Dr Becker. Is one justified in using the term pustular bacterid in cases in which one does not demonstrate bacteria in the lesions or in any focal infection? Is it not wiser to use a general term rather than to use a narrow term loosely? That is, might it be better to think of all these cases as of dyshidrosis, or would it be practical to call the conditions recalcitrant vesicular or pustular eruptions of the soles and palms and leave the mind open for future developments? I am not sure of the best answers to my questions.

DR EDWARD A OLIVER Recently, with the return of men from service, I saw a number of cases of hyperhidrosis of the palms and soles. In all of them the vesicle is much more superficial and not nearly as deep seated as this type of lesion is. Because one cannot find a focus of infection, it does not mean that Andrews was not correct in saying that if one removes the focus of infection the eruption will clear up. I have had a number of cases with definite foci of infection in which, on removal of the focus, the eruption cleared up.

DR FRANCIS E SENEAR I cannot think of anything in which there is more confusion than in the diagnosis of eruptions of the hands. I would like to ask Dr Becker, because I think he is confusing me more, how one reconciles a condition like dyshidrosis, which is a recurrent disease, with one which is so chronic or so recalcitrant as is the pustular bacterid type of infection. I agree with Dr Lynch. I like the term recalcitrant eruption because it does not commit one to anything. I wonder whether Dr Becker meant that ordinary dyshidrosis in the Tilbury-Fox sense eventually becomes chronic and of the recalcitrant type. The outstanding characteristic of these recalcitrant eruptions is that there are flattened lakes of pus with a different type of eruption than that seen in dyshidrosis. I would like, if I am going to be further confused, to know in which direction to carry my confusion.

DR S W BECKER I think that there is more difference of opinion about this particular type of eruption than about any seen in dermatologic practice. I remember the statement Dr Peck made when Andrews read his paper at the American Medical Association meeting in Milwaukee. The accumulations of leukocytes in the vesicles are epidermal, there is no erythema about them, they are different from infected lesions. I have seen patients who had what would be called ordinary dyshidrotic lesions which became infected, as a result of which the vesicles were surrounded by erythema and were under tension. I am not prepared to state why some patients present clear vesicles and some pseudopustules. We may be dealing with two entirely different diseases, but I do not know how to distinguish them.

DR FRANCIS W LYNCH Tilbury-Fox in his original description mentioned that in certain cases the dyshidrosis becomes chronic. The chronic condition he had in mind is evidently not what most of us have in mind today when we use the term dyshidrosis.

DR MICHAEL H EBERT This type of case presents a problem in nomenclature rather than in diagnosis. We are all familiar with this entity. It is a recalcitrant eruption characterized by lakes of pus which dry and scale, leaving an erythematous surface with a predilection for the soles and palms. A few days ago this young woman presented pustules on both hands and feet. Today only scaly relics are present. It is a question whether this disease should be designated a bacterid, a recalcitrant eruption or pustular psoriasis. In some cases the presence of psoriasiform lesions along the areas, with an eruption identical with this on the palms or soles, makes a diagnosis of pustular psoriasis a likely one. In such cases one should search for foci of infection. If their removal results in cure it would seem that the disease is a bacterid. This girl has such a focus in her tonsils. These will be removed with, I hope, good results.

Lichen Striatus Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR J GARFFIN

Lichen Planus Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR J GRAFFIN

A Case for Diagnosis (Dermatitis Atrophicans?). Presented by DR HERBERT RATTNER and (by invitation) DR H RODIN and DR N L BAKER

Pseudoxanthoma Elasticum Presented by DR MICHAEL H EBERT and (by invitation) DR N L BAKER

C B, a white woman aged 62, about twelve years ago noticed that the skin of the neck began to sag and she could stretch it rather freely. Then the skin over the arms, legs and abdomen took on a peculiar pitted appearance and yellowish color. There have been no other symptoms, and she has been in good health.

The sides of the neck, flexor surface of the arms and legs, axillas, abdomen and thighs are involved in the process, the skin over these areas is extremely lax, pitted and yellow. The ophthalmologist reported that there were no angioid streaks seen on the retina.

The roentgenographic examination of the chest showed mild atheromatosis of the aorta and calcification in the trachea and main bronchi. The total cholesterol of the blood serum was 196 mg per hundred cubic centimeters (within normal limits), the cholesterol esters were 41 per cent (50 to 75 per cent is normal) and the total blood lipids were 0.79 Gm per hundred cubic centimeters (0.57 to 0.82 is normal). The albumin-globulin ratio and the total blood proteins were normal, the fasting blood sugar was 90 mg per hundred cubic centimeters. The alkaline phosphatase and blood calcium were normal. The histologic examination showed typical changes of pseudoxanthoma elasticum.

DISCUSSION

DR M J REUTER, Milwaukee This is an unusual case and is the most extensive involvement with pseudoxanthoma elasticum that I have seen. The skin is lax and thrown into folds but is not hyperelastic, because if the skin is

stretched it does not fall back into place. Cutis hyperelastica and Ehlers-Danlos syndrome were the diseases that I considered in the differential diagnosis. Clinically the yellowish white papules suggest pseudoxanthoma elasticum, with the final diagnosis dependent on the results of the microscopic examination.

DR CARL W LAYMON, Minneapolis. This is the most extensive involvement with pseudoxanthoma elasticum I have ever seen. I, too, felt at first that it might be an example of the Ehlers-Danlos syndrome. There was no tumor formation. As Dr Finnerud suggested, one must not regard pseudoxanthoma elasticum as a cutaneous disease only because there may be changes in all of the elastic tissues of the body. Since one finds calcification in the skin in pseudoxanthoma it is not surprising that it may also be found in the lung. The skin in pseudoxanthoma elasticum looks like that of a plucked chicken, a clinical feature which is of value diagnostically.

Xanthoma Tuberosum Presented by DR MICHAEL H EBERT and (by invitation)
DR M S KAGEN

S P, a white man aged 31, had yellowish nodules on his elbows, knees and heels ten years ago. Several lesions on the elbows gradually enlarged to the size of a marble, and two tumors were excised on the left elbow.

On March 13, 1946, the patient was found to have a total blood cholesterol of 800 mg per hundred cubic centimeters, and he was given an animal-fat-free diet at that time. On April 2, 1946, the total blood cholesterol had dropped to 740 mg per hundred cubic centimeters and the lesion on the right elbow appeared smaller. The results of the physical examination were entirely negative except for the xanthomatous lesions. The histologic examination showed typical changes of xanthoma tuberosum.

DISCUSSION

DR STEPHEN ROTHMAN. The patient also had tendon xanthomas. In all these cases there is disturbance of the lipid metabolism. It is unusual to see pedunculated xanthomas, and I wonder whether the lesion of the elbow is not a simple fibroma. In one of my cases of generalized xanthomatosis the eruption cleared up and the blood lipid values returned to normal during pregnancy. After delivery the patient relapsed. The administration of progesterone was ineffective. Effective treatment for xanthoma tuberosum is local ultraviolet irradiation.

DR THEODORE CORNBLEET. This patient was given dietary therapy, resulting in a moderate decrease in the blood cholesterol. Such a small decrease could be accounted for, I believe, in the ordinary fluctuations of the lipid levels. My experience with dietary therapy has not proved this approach to be effectual. I have followed carefully patients with xanthomatosis with both raised and normal levels of blood cholesterol, without finding any decisive clinical or laboratory changes.

DR CARL W LAYMON, Minneapolis. I want to corroborate what Dr Cornbleet said. One reads in the literature that the response to a low fat diet in xanthoma tuberosum is good, but in my experience it has been disappointing both clinically and in reduction of the cholesterol blood level.

DR STEPHEN ROTHMAN. Low cholesterol diet is obviously ineffective, because cholesterol is synthesized in the body as shown in experiments with labeled carbon atom compounds by the Harvard group.

DR ROBERT L BARTON (by invitation). I would be interested to know whether in Dr Rothman's cases the blood fats showed great improvement.

DR STEPHEN ROTHMAN I had 1 diabetic patient that improved

DR FRANCIS E SENEAR I was interested in what Dr Rothman said about the endocrine aspect An internist showed me a patient that he had cured with thyroid extract This was the second case he had and he was publishing reports of them It is apparent from those 2 instances that it is worth considering the endocrine aspect

DR THEODORE CORNBLEET Thyroid has been given a trial in this patient without causing any improvement In any case, however, I believe that thyroid should be tried

A Case for Diagnosis (Erythema Figuratum Perstans, Erythema Annulare Centrifugum [Darier]?). Presented (by invitation) by DR MAURICE OPPENHEIM and DR D COHEN

A Case for Diagnosis (Pityriasis Rubra Pilaris?) Presented by DR EDWARD A OLIVER and (by invitation) DR A B HENNINGSSEN

Onychomadesis Presented by DR FRANCIS E SENEAR

Koilonychia with Dystrophic Nail Changes Following Gastric Resection
Presented by DR STEPHEN ROTHMAN and (by invitation) DR A L SHAPIRO

C C, a white man aged 20, had a splenectomy at the age of 6 because of repeated hematemesis and melena due to Banti's syndrome He subsequently had esophageal and gastric varices The varices in the esophagus were treated with injections of sclerosing solutions, but hemorrhages from the gastrointestinal tract continued On Aug 31, 1944, a total gastrectomy was performed Since then he has had only one hemorrhage, on Feb 5, 1945

About two months after the operation the patient noticed transverse bands on the nails A few months later dystrophic nail changes developed and progressed When seen in the Dermatology Clinic of the University of Chicago on March 30, 1946, he presented flattening and a tendency to concave curving of all finger nails, onycholysis with loss of large parts of the plate of the right first and second and left third fingers and transverse white bands on left fourth and fifth finger nails There was exaggerated koilonychia of the right second and left fifth toe nails and an onycholytic distorted right great toe nail

On March 29, the erythrocyte count was 4,630,000, hemoglobin 10.5 Gm and leukocyte count 13,050, the differential count showed 64 per cent polymorphonuclear leukocytes, 18 per cent large lymphocytes, 14 per cent monocytes, 1 per cent eosinophils, 2 per cent basophils and 1 per cent stab forms There was considerable hypochromasia and moderate anisocytosis of the erythrocytes In July 1944 the Kahn reaction of the blood was negative

DISCUSSION

DR FRANCIS W LYNCH, St Paul In this instance I think that there is a disturbance in the growth and the metabolism of the nail itself, undoubtedly associated with some systemic disturbance I think that most dermatologists now realize that such thinning and brittleness of the nails are related to a disturbance in iron metabolism In this case there is rather considerable hypochromic anemia Nail changes of this type are probably not associated with hemoglobin deficiency, but rather with some disturbance in the absorption and metabolism of iron

This case can well be contrasted with the preceding one in which the disturbance is in the growth of the nail rather than its metabolism. I think that it is less likely that there is an association with any systemic disturbance, since the nail seemed to be produced at the normal rate. The defect there is some disturbance in the attachment of the nail to the nail bed, since the nail and the bed separate as the nail progresses slowly and distally over the nail bed.

DR FRANCIS E. SENEAR: I think that we appreciate what Dr. Lynch pointed out. That is the reason I rather like this name, onychomadesis, because the nail formed normally and fell off. I would rather use that name than onycholysis because there is no destruction of the nail.

DR THEODORE CORNBLEET: Koilonychia may be a part of the Plummer-Vincent syndrome, in which dysphagia may be prominent. Iron metabolism may be a factor.

DR ROBERT L. BARTON (by invitation): In supplementation of what Dr. Lynch said about iron therapy, the internists are enthusiastic about iron therapy in anemias of women approaching the menopause in whom koilonychia is a frequent sign. With this boy's losing a considerable amount of blood and having had a gastrectomy, I believe, as Dr. Lynch does, that the koilonychia may be attributable to his iron deficiency anemia.

DR STEPHEN ROTHMAN: I do not know whether there is a special Plummer-Vincent's syndrome. It seems rather that any kind of hypochromic anemia elicits such nail changes.

Pemphigus Erythematosus (Senear-Usher Syndrome) Presented by DR R. H. SCULL

E. P., a Negro aged 41, presents a condition that began eight months ago on the scalp and on the face, later involving the back and chest. The condition of the scalp favored that of seborrhea, while that of the face resembled lupus erythematosus. The lesions of the chest and back were circumscribed papular crusting discrete lesions such as are present today.

This patient was presented to the Chicago Dermatological Society and to the American Dermatological Association as having pemphigus foliaceus in 1940. He was treated with acetarsone. After a few months the lesions cleared up. While the patient was under observation and receiving treatment, the eruption present today developed. The results of the laboratory examinations were normal. A biopsy showed acanthosis of the epithelium with sloughing off of the hyperkeratotic and dyskeratotic layer. In the corium there was a perivascular infiltrate, mostly of lymphocytes.

DISCUSSION

DR OLIVER S. ORMSBY: I think that the patient presents the triad of symptoms which belong to pemphigus erythematosus, namely, a lupus-like eruption on the face, seborrheic dermatitis in the scalp and bullous lesions on the body. Often the lesions on the body develop seborrheic dermatitis-like crusts. When one of these patients was first seen, about thirty-five years ago (*ARCH. DERMAT. & SYPH.* 4: 284, 1921), this type of case had not been previously described. That particular patient is still under observation, but for other conditions. This case, together with two others, was described later by Senear and Usher (*ARCH. DERMAT. & SYPH.* 13: 761, 1926). We considered the condition benign at that time, which it has usually proved to be. The histologic structure in our original case, studied by Dr. Finnerud, showed pemphigus. Though

most of the lesions were considered to be benign, in some cases there was a malignant course. In the majority of cases a benign type of pemphigus is present.

DR EDWARD A. OLIVER. This case is similar in many respects to the case of pemphigus erythematosis that Dr. Zakon reported last month. This patient had severe pemphigus vulgaris first, as did his patient, and then this type of disease developed.

DR MAURICE OPPENHEIM (by invitation). I can see the Senear-Usher syndrome as a primary lesion of pemphigus in most of the cases. In this case the changes from malignant pemphigus foliaceus to the benign form could be caused by the acetarsone therapy. If one gives acetarsone to a patient with pemphigus one often changes the type of lesions. Instead of blisters and blebs there occur lichenoid and papular lesions without blisters.

DR MICHAEL H. EBERT. In this connection, it should be stated that there are exceptions to all rules in medicine. At present there is an exception to the rule Dr. Oppenheim just enunciated, that the clinical course of pemphigus foliaceus is changed by the proper administration of acetarsone. I have under observation at Cook County Hospital a young woman of 36, with what I should like to call malignant pemphigus vulgaris, of three and one-half months' duration. She has extensive bullae on the trunk and extremities and in the mouth. She is very ill. Acetarsone has been administered according to Dr. Oppenheim's formula. In addition, she had been given blood transfusions in order to keep the blood protein level as nearly normal as possible. Penicillin in large doses has been administered since admission. In spite of this, her temperature rose every day to 102 or 103 F. In spite of the acetarsone and all other medication, the course has been steadily downhill and has not been influenced in the least by any form of medication. (The patient died two months after the meeting.)

DR H. E. MICHELSON, Minneapolis. I think that those of us who see and have seen a good deal of pemphigus should occasionally state our impressions. As I think over the cases that we have had in the University Hospital, I am inclined to think that the resistance of the patients to the disease seems to be important. Patients who have little resistance die quickly in spite of any therapy, and the other type of patients responds to a great many preparations, such as arsenic, suramin sodium, transfusions and the like. I think that it should be emphasized that acetarsone, whether given according to schedule or not, is not a specific remedy. For my own part, I cannot believe that a schedule can be the important point in administration of this drug, for, if it were so specific in its action, it should affect the lesions when given in an adequate dosage. One must not forget its toxicity, and I presume that the schedule is drawn up with the hope of preventing accumulative action. Observers in the older literature brought out the point that the disease in those patients whose lesions crusted readily and remained dry had a better prognosis than in those whose lesions were wet and did not crust.

DR OPPENHEIM. I do not agree with Dr. Michelson. A fatal prognosis was made by Newman if pemphigus started in the mouth or in the genital area. He said that if pemphigus started in other parts of the body a benign type could be expected. Kaposi had the same opinion, and so did Hebra.

In the case mentioned by Dr. Ebert I would ask whether the acetarsone was administered in capsules. If there are oral lesions it is dangerous to use acetarsone, because the parenteral absorption of acetarsone is dangerous and

cutaneous rashes, high temperature and erythema will follow. In such cases the acetarsone must be given in capsules, so that absorption takes place in the intestinal tract. According to my long experience with pemphigus, there is now no better treatment. Vitamin D therapy, blood transfusions, suramin sodium and all other methods are merely additional methods.

A Case for Diagnosis (Keratosis Follicularis?) Presented by DR CLEVELAND J WHITE and (by invitation) DR ROBERT C RANQUIST and DR KENNETH BAKER

Nevus-Araneus-Like Telangiectases with Palmar Erythema Presented by DR S WILLIAM BECKER

Miss F B, a nurse aged 23, had had an erythematous lesion on the dorsal aspect of the terminal phalanx of the left middle finger as long as she could remember. She considered it a birthmark. Two erythematous papules developed on the right cheek in January 1943. In July 1944, they were desiccated, paled out for one week, and then recurred. They were retreated in 1945, while the patient was in the army, with no improvement. An additional lesion appeared on the dorsum of the left hand a year ago and a second one during the last ten months. Her palms for years have shown mottled erythema, and she believes that her soles have been somewhat red. The palms and soles have always perspired profusely, which she attributes at least in part to nervous tension. If her hands hang down, the palms become darker and the hands feel swollen. When she blows her nose, a little blood is produced, but there is no definite flow of blood.

At her recent discharge from the army, she was told that she had a deviated septum, but no mention was made of intranasal telangiectases. No one in the family has red palms or soles, a nevus-araneus-like lesion or severe nosebleed. She has always been in good health.

Examination showed the soles to be slightly erythematous, while the palms showed diffuse mottled erythema. The dorsal surface of the terminal phalanx of the left middle finger showed an erythematous nonelevated lesion from which blood could be expressed by pressure. On the dorsal surface of the left hand was a nevus-araneus-like lesion. On the dorsal surface of the right hand, there were three erythematous macules, from which blood could be expressed by pressure. On the right middle finger was nevus-araneus-like telangiectasis.

DISCUSSION

DR FRANCIS E SENEAR: The patient said she could detect pulsation.

DR THEODORE CORNBLEET: Was there anything found to show that the liver is at fault? Hepatic changes have been incriminated in some cases.

DR S W BECKER: I asked this girl to come here because she was worried for fear she might have some severe toxic disease. She has been discharged from the army just recently and has had several physical examinations. She has always been in good health and is a hard-working nurse. Her family history is irrelevant. It is difficult to make a diagnosis. I thought that Osler's disease was probably ruled out because of the absence of nasal bleeding. She has never been pregnant, so that pregnancy cannot be responsible for the appearance of the lesions. She has had palmar erythema for many years. I think that the patient has slight palmar erythema with lesions of the nevus-araneus type.

Monilethrix. Presented by DR STEPHEN ROTHMAN and (by invitation) DR M R ROBIN and DR Z FELSHER

Lichen Nitidus. Presented by DR FRANCIS E SENEAR and (by invitation) DR ADOLPH ROSTENBERG JR

Poikiloderma Vasculare Atrophicans Presented by DR STEPHEN ROTHMAN and (by invitation) DR A L SHAPIRO

M W, a woman aged 47, has always had a dry skin Ten years ago, while warming herself over a hot radiator, she noticed a rather sudden onset of a generalized erythematous eruption on her body In 1941 she visited the University of Chicago Clinics, where the diagnosis of poikiloderma vasculare atrophicans was made She had a reduction of sugar in the urine, but the glucose tolerance test proved this to be renal glycosuria The patient was presented before the Chicago Dermatological Society on Oct 15, 1941 (*ARCH DERMAT & SYPH* 45 800 [April] 1942)

Previous treatment, including arsenic and ultraviolet ray therapy, had been unsuccessful In our clinic thorium-x was applied to localized areas with only temporary slight improvement Bland ointments on the skin provided some relief of dryness

The patient returned to our clinic on March 27, 1946, after a lapse of four and one-half years and stated that there had been no essential change in her condition However, she was convinced that she improves just before and during her menstrual periods She presented a generalized erythematous dermatitis with telangiectases, depigmentation and areas of lichenification There was a fine diffuse scaling as well as localized patches with decided scaling There was moderate enlargement of lymph nodes The leukocyte count was 4,800 and the hemoglobin 15.8 Gm The Wassermann and Kahn reactions of the blood were negative

A biopsy of the left scapular region showed the horny layer to be of normal thickness with several parakeratotic sections The granular layer varied from 1 to 3 cells in thickness There was considerable edema in the basal layer and adjacent rows of cells and, to a lesser extent, intercellular edema of the remaining stratum mucosum The upper part of the corium showed extensive edema with considerable lymph space and blood vessel dilatation and proliferation and a predominantly lymphocytic perivascular infiltrate In one localized area the epidermis was completely disorganized up to a few cell layers of the surface by dermal edema and infiltrate There was collagen and elastic tissue degeneration in the upper third of the corium

DISCUSSION

DR EDWARD A OLIVER I think that this is a poikiloderma-like eruption I think that Dr Oppenheim will agree that the earliest changes are about the eyelids There is generally inflammation and edema of those parts I questioned this patient, and there was no evidence of that, nor was it mentioned in the history Furthermore, there was not the picture of roentgen-ray-like changes that are seen in poikiloderma

DR MAURICE OPPENHEIM (by invitation) There are many cutaneous diseases which can simulate the picture of poikiloderma What I have seen today is a clinical picture which does not fit the Jacobi type because there is no hyperpigmentation and no hyperkeratosis of the sebaceous glands Therefore, I

am a little doubtful I believe that we have to revise the whole picture of poikiloderma vasculare atrophicans There are many pictures, as Dr Oliver pointed out, which come under that type I do not believe that poikiloderma vasculare atrophicans is an entity

DR STEPHEN ROTHMAN I believe that Jacobi's description fits this case Telangiectases, especially over the breast, are present without any doubt The itching is due to xerosis and is relieved by greasing The long duration corresponds with Dr Oppenheim's description

Superficial Localized Scleroderma Presented by DR STEPHEN ROTHMAN and (by invitation) DR Z FELSHER

Tuberculosis Cutis Verrucosa Presented by DR MARCUS R CARO and DR JAMES HERBERT MITCHELL

H F Mc, a white man aged 56, burned the top of his left middle finger posterior to the nail about eight years ago when a package of matches exploded A red area remained at the site, a rough surface gradually developed, and it became heaped up This change has spread progressively over the entire finger to involve the area affected at present There has been no pain, itching or other symptoms At one time he received fourteen roentgen ray treatments locally without any improvement

The entire left middle finger is covered by a whitish diffuse verrucous mass the surface of which resembles a bas-relief map of mountains and valleys The nail is still present This finger is nearly twice the width of the others There is a sharply defined circinate border on the proximal phalanx which consists of a narrow band that is dull red and slopes up gradually into the verrucous zone The microscopic examination of scrapings failed to demonstrate any fungi

DISCUSSION

DR H E MICHELSON, Minneapolis This is unusually severe tuberculosis verrucosa cutis The patient received fourteen roentgen treatments without effect, and the question now is what should be done I believe that amputation is the best recommendation I would like to know the subsequent history

DR FRANCIS E SENEAR I think that amputation is the indicated treatment

DR THEODORE CORNBLEET In a recent issue of *The Journal of the American Medical Association*, the letter from England discussed the use of large doses of vitamin D in the treatment of lupus vulgaris I have been trying this method, but it is too soon to give an opinion as to its value One woman who has had considerable distress from large open fungating lesions has had temporary relief In this patient, however, if amputation is contemplated, it perhaps should not be delayed too long to forestall irreparable spread

DR ADOLPH ROSTENBERG Jr (by invitation) I thought that I heard the patient state that the condition fluctuated, that it gets better and then gets worse If that is so, it would be against the presenters' diagnosis

DR MAURICE OPPENHEIM (by invitation) Regarding what Dr Cornbleet said, I saw an article by Dr Charpy of Paris in which he stated that he had excellent results with vitamin D therapy in lupus vulgaris

DR STEPHEN ROTHMAN Should the diagnosis of tuberculosis verrucosa be confirmed the lesion should be removed because of the danger of dissemination of tubercle bacilli

DR MARCUS R CARO I want to apologize for presenting the case without another biopsy I think that before amputation is done he should have a complete physical examination, including a roentgenogram of the chest If no other lesions of tuberculosis can be demonstrated elsewhere, then amputation of the finger should be performed

A Case for Diagnosis (Dermatitis Herpetiformis Serpiginosus of Darier?)

Presented by DR FRANCIS E SENEAR

Mrs C O H presents an eruption which has been present intermittently for the past thirteen years The hands and arms alone have been involved for most of this time, but at one time the trunk was also extensively involved, with the lesions similar to those seen on the arms She stated that the lesions begin as "small blisters" These gradually enlarge by peripheral extension with a tendency to central clearing She has been treated by a number of physicians and has had treatment with ultraviolet rays, quinine, penicillin by injection (but not intensively), acetarsone and one of the sulfonamide drugs She stated that the acetarsone made her ill, while the use of the sulfonamide drug seemed to make the eruption worse A sulfonamide ointment applied locally made the eruption worse within two days She has also received calcium intravenously When the patient was first seen by me, on February 25, she presented on the dorsal surface of the hands and wrists a typical picture of nummular eczema, involvement being much more intense on the left hand The lesions on the forearm and arms were of a different type Here there were a number of lesions of varying size, the smallest being about $\frac{1}{2}$ inch (1.3 cm) in diameter and the largest about 2 inches (5 cm) in diameter While the patient has been under observation since that time, she has repeatedly had new lesions and it has been possible to watch them develop from a single pinhead-sized vesicle to the formation of patches 6 to 8 inches (15 to 20 cm) in diameter As peripheral extension takes place, the central portion of the lesion clears spontaneously The peripheral part of these annular arciform and gyrate patches presents moist oozing surfaces, in many places covered with a fairly thick yellowish crust

The eruption on the dorsal surfaces of the hands has practically cleared with the use of several short exposures to roentgen rays The lesions on the forearms have shown no tendency to improve with various local applications, including wet compresses of 0.25 to 1 per cent silver nitrate solution in the form of ointment, penicillin ointment and resorcinol (Lassar's) paste

DISCUSSION

DR STEPHEN ROTHMAN I thought that the picture was compatible with that of dermatitis herpetiformis serpiginosus described by Darier

DR S W BECKER I questioned this lady, and she said that many years ago she had an eruption on the sides of the neck I wonder whether this might not be related to so-called benign pemphigus

DR FRANCIS W LYNCH, St Paul The eruption always begins with small vesicles Might it not be possible to provide a watch crystal or some similar object which the patient could apply over the vesicle as a protection, so that the vesicle might remain intact until the patient comes to the clinic for bacteriologic investigation?

DR FRANCIS E SENEAR In view of what Dr Rothman said, the case is interesting, because the original Darier type of disease was not supposed to have

any vesiculation, yet the conception of that disease has been changed by the description by Gougerot and others of a vesicular type. It is also interesting that when Dr Oliver saw this patient with me in the office, without either one of us having any fixed idea of what it was, he suggested that possibly we might have to consider dermatitis herpetiformis. It is interesting that a number of good authorities, such as Brocq, have said that the erythema perstans group of the Darier type is really a form of dermatitis herpetiformis. Gougerot described a patient with erythema of the Darier type in whom typical dermatitis herpetiformis developed, while she continued to have the primary condition. I believe that the disease in this case is of the erythema perstans figuratum type. It represents a vesicular form of that disease.

I planned to give the patient arsenic as a therapeutic test, but, as indicated in the history, acetarsone has been given. I know nothing about the dosage or the method of administration employed with the latter drug, but its use made her extremely ill. Then she was given one of the sulfonamide drugs by a general practitioner, and this also made her sick, so that I was reluctant to use sulfapyridine, which some consider a diagnostic test for dermatitis herpetiformis. I should use arsenic in small doses, and, if she does not respond, sulfapyridine might be used.

Atrophoderma Reticulatum Faciei Presented by DR CLEVELAND J WHITE and (by invitation) DR JOHN W SMITH, Milwaukee

R G, a school girl aged 18, has had an eruption on the face of several years' duration. According to her history it starts as a small scale and, in the course of several months, it leaves a small scarred area. It has been progressive and now involves considerable areas of both cheeks.

The examination reveals an eruption involving the flush areas of the cheeks, most evident on the right side, consisting of a network of small irregular punctate atrophic areas. It apparently starts as a slight scaling dermatitis. Her general health has been good. There is a history of macrocytic anemia in November 1945, but the blood picture is now back to normal. There is no history of a similar cutaneous disease in any member of the family, and results of all the ordinary laboratory examinations have been normal. No biopsy has yet been performed.

DISCUSSION

DR FREDERICK R SCHMIDT: This is a disease appearing on the face and described as folliculitis ulerythematososa reticulata. There have been several cases reported. The lesions practically always begin between the ages of 7 and 12 years and disappear at 18 or 20, are definitely symmetric and appear as scaling red lesions. There are definite symmetric ridges between them, giving the eruption a reticulated appearance. In this girl the lesions have been confined to the right cheek.

Another factor that interested me and others is that, being on the right side, the lesions may have been induced by the patient.

DR CLEVELAND J WHITE: In 1916 Pernet described a syndrome which clinically is typical of the condition in the case presented. The lesions develop spontaneously and atrophy with a reticulated appearance. A delicate tracery encloses slight fibrous atrophic areas. Although there is an almost exact symmetry and there is clinically primary atrophy, the factitious element still has to be ruled out. A biopsy will be performed as soon as permission can be obtained from the patient and her parents.

NOTE—A biopsy was performed and the section sent to Dr Fred D Weidman of Philadelphia. He described it as showing an epidermal atrophy with inter-papillary pegs short and deformed. Dr Weidman stated that there is definite primary atrophy of the epidermis. There was no trace of an inflammatory reaction or fibrosis in the corium. He stated that the observations at biopsy are compatible with this clinical diagnosis. It would be a difficult situation to explain if the patient had a lesion of this type after having had low voltage roentgen ray therapy for a dermatologic lesion.

Marcus R Coro, M D, *President*

Leonard F Weber, M D, *Secretary*

May 16, 1946

A Case for Diagnosis, Ulcers of the Legs Presented by DR THEODORE CORNBLEET and (by invitation) DR D COHEN and DR N L BAKER

Stomatitis (Bismuth?) with Ulceration Presented by DR THEODORE CORNBLEET and (by invitation) DR J GRAFFIN and DR D COHEN

Superficial Epitheliomatosis Presented by DR HERBERT RATTNER and (by invitation) DR J GRAFFIN

E C, a white man aged 60, in 1938 noticed a pea-sized lesion on the right cheek, which slowly grew to its present size. It never became ulcerated. In 1939 he noticed another lesion on the dorsum of the right hand. Later, in 1943, there developed a red scaly lesion in the left infraclavicular region, and about one year ago there appeared a reddened area on the left thigh.

The patient acquired syphilis in 1905, for which he was treated with arsenicals by mouth for three years. He now has clinical signs of tabes dorsalis, for which he has had continuous treatment with arsenicals and bismuth salts from 1940 to March 1946.

On the right cheek there is a 3 by 2 cm lesion with a rolled border. In the central portion of an atrophic area is a single nodule. On the right hand there is a 2 by 1 cm erythematous lesion. On the left infraclavicular region there is a 5 by 4 cm erythematous and scaly patch with a central hard nodule. On the left thigh there is a scaly patch 1 by 1 cm.

The Kahn and Wassermann reactions of the blood were negative. The Wassermann reaction of the spinal fluid was negative, the reaction to the Pandy test was negative, the cell count was 0, and the colloidal gold curve was 1111110000. Examination of the blood showed 4,500,000 erythrocytes, 84 per cent hemoglobin and 8,200 leukocytes. The urine was normal. The roentgenogram of the chest was normal. The nonprotein nitrogen was 46 mg per hundred cubic centimeters.

Several specimens were removed for histologic examination. Several showed a superficial basal cell epithelioma. In one there were Bowen-like changes in the epidermis. In another there were Bowen-like changes in the epidermis, and just beneath this area there were many nests and linear strands of basal cell epithelioma in the upper and middle parts of the corium.

DISCUSSION

DR HAMILTON MONTGOMERY, Rochester, Minn. There were four or five different specimens for biopsy. Some showed basal cell epithelioma and others

basal squamous cell, and one section was that of a squamous cell epithelioma, grade 1, with Bowen-like changes. We know that arsenic is a carcinogenic agent. In the majority of patients with superficial epitheliomatosis, the lesions are basal cell in character. This man represents a combination of superficial epitheliomatosis and superficial epithelioma due to arsenic. He not only had arsenic by mouth but also arsphenamine, which usually does not produce epidermal changes and is usually not regarded as carcinogenic. Many years ago Dr. Ebert produced a cutaneous cancer experimentally with arsphenamine. Many dermatologists will not treat syphilitic leukoplakia with arsphenamine because they feel that this increases the incidence of cancer superimposed on the leukoplakia.

DR. MARCUS R. CARO: In one of the sections there were changes which I had never seen before. There were Bowen-like changes in the epidermis, and in the corium beneath this area lay many strands and nests of basal cell epithelioma.

Dermatitis Medicamentosa (Purpuric) Presented by DR. THEODORE CORNBLEET and (by invitation) DR. J. GRAFFIN

Carcinomatosis of the Breast Presented by DR. HERBERT RATTNER and (by invitation) DR. N. L. BAKER and DR. J. GRAFFIN

Hidradenitis Suppurativa Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD D. OMENS and DR. N. L. BAKER

L. B., a Negro woman aged 33, had "boils" in the right axilla five years ago. A few weeks later, similar lesions appeared in the left axilla. The left axillary lesions cleared up in six months, leaving scars. About three years ago, the medial aspect of the thighs became involved at the upper third, with ulcers which healed after a few months and then broke down again.

There are hypertrophic scars in the left axilla and similar scars with interspersed draining sinuses in the right axilla. About the external genitalia and the upper third of both thighs, on the medial aspect, there are numerous dirty irregular shallow ulcers, with some bridging scars. On the left buttock there is a granulomatous tumor, 2 cm. in diameter. There is no rectal stricture.

Examination of the blood showed 3,000,000 erythrocytes and 11,000 leukocytes. The Kahn reaction of the blood was negative. The electrocardiogram and the roentgenogram of the chest were not remarkable. The lygranum cutaneous test resulted in an elevated infiltrated erythematous papule, 1 cm. in diameter. The Mantoux test, in dilution of 1:10,000, elicited a weakly positive reaction. Pus from a sinus was examined with Ziehl-Neelsen stain, but no tubercle bacilli were found.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This patient showed the characteristic features of hidradenitis suppurativa. In some instances there are also widespread deep-seated acne and pyogenic lesions of the scalp, nucha and upper part of the trunk. The condition may be associated with blue-domed cysts of the breast in obese women and with pilonidal cysts. Such cases often come to the attention of the proctologist or surgeon before the over-all picture is recognized by the dermatologist. I regard hidradenitis as an expression of acne in an exaggerated form; it seems that many of the contributing factors are present in both diseases. The only effective treatment is the extirpation of the purulent pockets, and this requires excision of the infected sites with removal of the glandular tissues. Penicillin and the sulfonamide drugs are useful adjuncts, but

they will not eliminate the infection here any more than they will in cases of pocketed empyema, without adequate drainage. At the same time the general health should be considered, and if obesity is present a program of weight reduction should be instituted. In the case of early infection of the axillas, for example, the lesions respond to simple drainage, but usually the area must be excised to prevent recurrence.

DR MAURICE OPPENHEIM (by invitation) I would like to make a therapeutic suggestion. The condition does respond well to roentgen ray therapy, but one must use relatively high dosages. I have cases in mind in which this treatment has succeeded, all other treatment, such as surgical excision, was not successful because there was not enough depth of penetration.

DR LOUIS A. BRUNSTING Roentgen therapy will help to reduce the inflammatory reaction and is an aid in treatment comparable to the use of penicillin or the sulfonamide drugs. Preferably filtered roentgen rays should be used, but it is my experience that after these preliminary measures surgical procedures are still necessary to effect a permanent cure. New lesions that develop can be treated symptomatically or destroyed when they are small. Long-standing burrowing processes in the axillas are best treated by excision and skin grafting.

DR MINNIE O. PERLSTEIN I was under the impression that this patient had a positive reaction to a Frei test. She still has a positive reaction to an intradermal test on the left forearm. The picture is compatible with that which is seen in lymphogranuloma venereum of the ulcerative type. I would like to suggest that as a diagnosis in this case.

Acute Disseminated Lupus Erythematosus with Relapse in a Woman
Aged 28 Presented by DR DAVID V. OMENS and (by invitation) DR HAROLD D. OMENS and DR N. L. BAKER

Chronic Discoid Lupus Erythematosus with Chilblain Lupus Presented by DR EDWARD A. OLIVER and (by invitation) DR SAMUEL BLUEFARB

The patient, a white man aged 35, first noticed an eruption involving the nose and cheeks about five years ago. It next spread to involve the neck and upper part of the chest. With treatment the lesions of the chest and neck cleared and there was improvement of the lesions on the nose and cheeks. A period of exacerbations and remissions followed, with extension of the process to involve the ears and lips. During this time, the patient said that he noticed some tenderness and burning of the finger tips and toes.

About two months ago there was a pronounced exacerbation with the appearance of the present lesions on the hands and feet.

Lupus Erythematosus Disseminatus Presented by DR FRANCIS E. SENEAR and STAFF

A B, a white girl aged 20, who had previously been hospitalized in an acute phase of disseminated lupus erythematosus, was readmitted complaining of a recurrence of joint pains and fever. The examination revealed superficial erythematous patches on both cheeks. There were erosive lesions of the gingival membranes. Irregularly outlined purplish red slightly raised flat lesions were present on the extensor surfaces of both arms. The finger tips were red, and bright red macules were present on the palms.

DISCUSSION OF CASES OF LUPUS ERYTHEMATOSUS

DR OLIVER S ORMSBY I would like to discuss the first case. The patient presented mild lupus erythematosus of the face. It did not appear at all serious, but this patient might have a flare-up with general dissemination that may end fatally. I have seen several patients who had a comparatively mild form of the disease with moderate symptoms. They had a temporary cessation of the symptoms and remained well for some months, and then the disease recurred with disseminated lesions, within a comparatively short time the disease terminated fatally. This woman's blood picture showed a leukocyte count a little below normal, but she did not have definite leukopenia. She did, however, have arthritis and other signs. While the patient presented a benign appearance today, I think that the outlook is serious.

DR H E MICHELSON, Minneapolis I object to the term chilblain lupus. The term lupus pernio is well established in the literature and is a form of sarcoid, but Dr Fox told us in New York recently that there was no place in the classification where this nomenclature could be used. The chilblain lupus of Hutchinson is probably a different disease entirely. It is interesting to note that in 1 of the patients there is much destruction of the ear lobe, in this particular locality, lupus erythematosus can sometimes be just as destructive as lupus vulgaris.

DR MARCUS R CARO Yesterday I saw a girl of 15 who for the past four weeks has had lesions of disseminated lupus erythematosus on the face and also a few lesions on the fingers. When I told the mother that it was an early case of lupus erythematosus, she informed me that the twin sister of this child had died of disseminated lupus erythematosus about two years ago.

DR EDWARD A OLIVER In answer to Dr Michelson, the picture in my case corresponds with the various textbook descriptions of chilblain lupus, and I believe it to be this and not lupus pernio. The patient still is a sick man, despite the fact that he has had considerable treatment with gold compound. He is now receiving nicotinic acid, 100 mg three times daily, with weekly injections of colloidal gold sulfide.

Exfoliative Dermatitis of the Newborn Presented by DR. DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR J GRAFFIN

Pityriasis Rosea with Involvement of the Face Presented by DR. THEODORE CORNBLEET and (by invitation) DR H SCHORR and DR N L BAKER

Xanthoma Tuberosum Presented by DR MAURICE OPPENHEIM (by invitation)

E S P, a white man aged 30, presents on the knuckles of both hands, the metacarpal and carpal joints sharply limited, mostly round contoured tumors, varying in size from that of an almond to that of a bean, orange yellow and movable on a normal base. The three larger ones have a central depression and are surrounded by smaller yellow tumors to form rings. The consistency is hard, similar to that of cartilage. The surface of the skin is shiny and not tender. Over the extensor surface of the metacarpal and carpal joints there are two scars the result of surgical treatment. On the interphalangeal joint of the middle finger of the right hand and under the finger of the left hand there are two tumors, as hard as bone, round and the size of a hazelnut, which are not yellow and which look like juxta-articular nodes. On the right elbow there is a scar, and on the

right side of the scar there is a tumor similar to the one on the hands. On the left elbow there is also a scar. On the patella there is a ring of yellow nodules, the size of a hemp seed, each nodule separated by a furrow. On the right palm there are two crescent-shaped lesions of similar consistency. The mucous membranes and other parts of the body are free.

The tumors first appeared fifteen years ago on the dorsal aspect of the left hand. The patient consulted many physicians and was treated surgically and by electrocoagulation. His mother had knots on her joints. A histologic examination made in New York in 1938 revealed xanthoma tuberosum.

The urine was normal. Chemical examination of the blood revealed sugar 140 mg and cholesterol 240 mg per hundred cubic centimeters, and lipids 785 mg per hundred cubic centimeters of blood and 1,170 mg per hundred cubic centimeters of plasma. The quantitative determination of sugar in a twenty-four hour specimen of urine was 2.4 Gm. The sugar tolerance curve after 100 Gm of dextrose were given showed per hundred cubic centimeters: 86 mg before intake (urine normal), 132 mg after $\frac{1}{2}$ hour (0.2 per cent), 118 mg after 1 hour (0.2 per cent) and 102 mg after 2 hours (normal).

DISCUSSION

DR CARL W. LAYMON, Minneapolis: I thought that this was an example of xanthoma tuberosum, although I was surprised that the blood lipids were not higher as is usual in these cases. Regarding therapy, we have all read reports about the value of an animal fat-free diet, but in the cases in which my colleagues and I employed this diet we were disappointed. In 1 man who had lesions on the palms, there was a loss of weight of 30 pounds (14 Kg.) on the diet and there was no effect on the xanthomas.

In some cases of diabetic xanthoma lesions are seen which are similar clinically to xanthoma tuberosum. I think that Dr. Montgomery will agree that histologically the lesions are the same, yet in diabetic xanthoma there is definite favorable response to diet and control of the diabetes.

DR THEODORE CORNBLEET: I, like Dr. Laymon, have found low fat diets ineffective therapy for the xanthomas. My observations on a number of patients using tests of hepatic function were not immediately illuminating. The subject of the liver and xanthomatosis is a large one and needs extensive discussion.

DR HAMILTON MONTGOMERY, Rochester, Minn.: The effect of an animal fat-free diet on lesions of xanthoma varies considerably. One cannot expect to see involution in old fibrous lesions. The small and newer lesions frequently respond to an animal fat-free diet. It is important to remember that about 40 per cent of the patients with xanthoma tuberosum have an associated cardiovascular disease, either angina pectoris or an obliterative vascular disease of the extremities. There is also a hereditary factor, and these patients are usually in the younger age group. They often get along well on an animal fat-free diet as far as the heart is concerned. Such a diet is readily supplemented with the necessary vitamins.

DR UDO J. WILE, Ann Arbor, Mich.: There is some misconception about the effect of diet as we at Ann Arbor carried it out in the therapy of xanthoma tuberosum. It was not our thought or practice to exclude animal fat, since it has been shown that disorders of lipid metabolism are not proportionate to the ingested fats. Our patients improved on a sharp reduction in total calories, and the fats were not proportionately decreased more than the proteins and carbohydrates. The present case is interesting in this connection since it should be noted that the patient had a high content of lipids in the blood and a relatively

low cholesterol content Our thought in reducing the entire diet was that these patients could withdraw the accumulated fats in the xanthoma lesion on a low intake, and we found that this could not infrequently be achieved

Bowen's Disease Presented by DR STEPHEN ROTHMAN and (by invitation)
DR A L SHAPIRO

J E, a white man aged 60, was always in good health In 1941 he was treated for rosacea in the University of Chicago Clinics About two years ago he noted a nonsymptomatic lesion on the right arm On April 29, 1946, examination revealed this lesion to be a roughly oval patch, 8 by 12 mm in diameter, fairly sharply demarcated, scaling and yellowish red There was a palpable infiltration of the lower border

The histologic section revealed a hyperkeratotic stratum corneum The stratum granulosum consisted of 1 to 2 cell layers The structure of the malpighian layer was greatly disturbed The cells varied in size and shape, many had no nuclei, and some were multinucleated Mitotic figures were scarce There were shrunken and clumped nuclei, and there was vacuolization of cells The normal palisade arrangement of the basal layer was lost There was dilatation of the blood vessels, edema and a dense predominantly lymphocytic infiltrate in the papillae and superficial corium On April 29, the leukocyte count was 6,100 and hemoglobin 14.6 Gm The urine was normal The Wassermann and Kahn reactions of the blood were negative

DISCUSSION

DR HAMILTON MONTGOMERY, Rochester, Minn I do not believe that this is Bowen's disease, nor is there sufficient histologic evidence to warrant such a diagnosis Whereas there are a few benign dyskeratotic cells, there is insufficient evidence to warrant a diagnosis of squamous cell epithelioma with Bowen-like changes In Bowen's original case there were arciform configuration of the ulcers, and the lesion resembled noduloulcerative syphiloderm Darier and later Frazer reported multiple lenticular plaque type lesions, but Frazer's patient on review had a history of ingestion of arsenic, so that it might well have been a superficial epithelioma due to arsenic and not Bowen's disease

DR OLIVER S ORMSBY I would like to corroborate what Dr Montgomery said Clinically the lesions in Bowen's original cases were described as a patchy eruption composed of lenticular papules and nodules resembling a noduloulcerative syphiloderm The early lesion was a pale red raised flat papule with a thick horny layer covered with a cornified crust Beneath the crust the surface might be red and oozing and granular or slightly papillomatous There was an annular or serpiginous configuration to the plaque with peripheral extension and central involution The histologic diagnosis by Bowen and others was a benign disease Since then many cases have been recorded in which the lesions were malignant Darier later described a second type of Bowen's disease in which there were multiple nonelevated scales or lenticular plaques The histologic picture as originally described by Bowen has been repeatedly confirmed Today, in discussing epithelioma, one discussor spoke of Bowen-like changes Superficial epitheliomatosis sometimes shows these changes These, however, do not constitute Bowen's disease Clinically Bowen's disease presents the picture just described

DR. CLARK W FINNERUD I thought clinically that it was a morphea type of epithelioma Histologically it is not Bowen's disease

A Case for Diagnosis (Erythema Bullosum?). Presented by DR FRANCIS E SENEAR and STAFF

A Case for Diagnosis (Lymphoblastoma? Lichen Planus?). Presented by DR EDWARD A OLIVER, DR. JAMES R WEBSTER and (by invitation) DR H S STEINBERG

Mycosis Fungoides Presented by DR. FRANCIS E SENEAR and STAFF

J W, a white man aged 60, was readmitted to the Dermatology Service, University of Illinois Research and Educational Hospital, in a cachectic state, exhibiting multiple ulcerating nodules scattered on the skin. A diagnosis of mycosis fungoides had been made one year previously and roentgen ray therapy ordered. He has recently become refractory to roentgen treatment, and many new ulcerating nodules have appeared. Sternal marrow puncture and studies of the peripheral blood have revealed no abnormalities except for a variable degree of eosinophilia.

DISCUSSION

DR UDO J WILE, Ann Arbor, Mich. I would like to ask Dr Senear what the histologic picture showed.

DR FRANCIS E SENEAR. The histologic picture was more that of leukemia, but the clinical condition from the start appeared to be mycosis fungoides. Bullae and some other changes were present in the section.

DR UDO J WILE. I should like to express again the view which the late Dr Pusey frequently insisted on, that mycosis fungoides is a clinical picture. In any particular case which clinically fitted this disease one might find any microscopic picture.

Indeed, I have seen in the same patient three different histologic pictures from three clinical lesions. In other words, there is no microscopic picture which can be said to be entirely typical of mycosis fungoides.

The cell types in all cases, however, are usually embryonal. Great variation can occur with mutation in the cell type not only spontaneously but under the influence of roentgen therapy. The remark that Dr Pusey made that mycosis fungoides is a clinical picture was a sapient one.

DR FRANCIS E SENEAR. I would like to recall that on the occasion of the first presentation of this man, we spoke of our experience with the histopathologic studies on the lymph nodes in another patient who had what we regarded as possibly a leukemic id. Three pathologists went over the slide, one thought that it was a node from a case of leukemia, the other a lymphosarcoma and the third man said that he would be unwilling to classify it. We have had exactly the same experience with the cutaneous histologic picture in this case as in the other.

Extensive Lichenification of Perineum, Penis and Scrotum Presented by DR EDWARD A OLIVER, DR JAMES R WEBSTER and (by invitation) DR H S STEINBERG

Lymphangioma Circumscriptum Presented by DR FRANCIS E SENEAR and STAFF

Urticaria Pigmentosa Presented by DR HERBERT RATTNER and (by invitation) DR. MARTHE ERDOS-BROWN

Amyloidosis Cutis Presented by DR FRANCIS E SENEAR and STAFF

A S., a married white woman aged 53, had a history of asthma and hypertensive cardiovascular disease of two years' duration. For the same length of time, an extensive pruritic eruption had been present, beginning on the extensor surfaces of the legs and spreading to the lower part of the back. No medication had affected the objective appearance or associated pruritus.

On examination at the Illinois Research and Education Hospital Dermatology Clinic on May 13, 1946, she presented ill defined bilateral symmetric plaques of the pretibial surfaces, consisting of firm yellow-brown, pea-sized papules, some of which tended to coalesce. A similar plaque was present in the low back region. Ill defined lichenified areas existed on the extensor surfaces of the elbows, and there was one such area on the right arm. No apparent mucous membrane lesions were present. One per cent aqueous solution of congo red was injected subcutaneously into the substance of the lesion on the legs.

A biopsy from the back showed a microscopic papule which was covered by a thick nonnucleated scale. The granular layer was intact, and the rete pegs were elongated to separate greatly widened papillae. These contained masses of homogeneous material with a few cells within them. With the Van Gieson stain these masses were grayish yellow.

DISCUSSION

DR H E MICHELSON, Minneapolis. The subject of amyloidosis is a difficult one, and dermatologists have a difficult time arriving on a common ground with the internists who see generalized amyloidosis but not with cutaneous involvement. The disease which Dr Lynch and I reported involved the tongue and the muscles and also the skin secondarily, especially at the finger tips and about the face. Dr Laymon gave a number of injections with congo red solution to see whether other diseases might not give a positive reaction, but he did not find this to be the case. One must be careful in staining for amyloid because no two sections seem to take the stain exactly alike, and it is always well to have a positive control.

DR LOUIS A BRUNSTING, Rochester, Minn. In systematized amyloidosis there is a close relationship between amyloid, Bence Jones protein and multiple myeloma, occasionally the atypical plasma cells or myeloma are demonstrated only in the sternal bone marrow. I would recommend a sternal biopsy in this case, although the process is not of the systematized type. While most of the lesions were present over the tibia, there seemed to be a scattering of questionable nodules in the skin of the back.

The Nomland congo red test to demonstrate amyloid in the skin is a valuable procedure, but the intravenous technic of Bennhold or Paunz should be used with caution in cases of widespread amyloidosis. In 1 patient with systematized amyloidosis who was given an intravenous injection of congo red, the entire skin became tinted pink and the small nodules a dark red, and at necropsy two months later, the skin and the musculature of the heart and gastrointestinal tract were still tinted a healthy pink.

DR FRANCIS E SENEAR. We saw this patient only two days ago, and we hastened to make a biopsy so that she could be presented. We had no opportunity to do as much special staining as we would like. She presented a peculiar picture. In addition to the lesion present previously on the tibia, which would suggest an amyloid type of degeneration, she had a pronounced eruption in the sacral region and particularly over the ribs which looked like an ordinary type of verruca. This eruption looked so much like verruca that I spoke at the time about a consideration of some of the verrucous diseases which have interested us lately, such as acrokera-

tosis and the epidermal dystrophy type of lesion. In addition, she had a lichenification which would be difficult to reconcile with the verrucous disease. These individual lesions are so much of that type that I realize we are presenting the patient without adequate preparation. I would like to ask Dr. Caro to say a word about the congo red test.

DR. MARCUS R. CARO: On histologic section the congo red stain did not show any selective staining in the hyalinized masses in the papillary layer. With the Van Gieson stain one could see grayish yellow masses at this site which suggested either amyloid or some other degenerative process. I am not sure about the results of vital staining with congo red in this case, for there was diffuse staining of the entire area of injection.

A Case for Diagnosis, Possible Lupus Erythematosus Presented by DR. FRANCIS E. SENEAR and STAFF

Dermatomyositis Presented by DR. FRANCIS E. SENEAR and STAFF

P. S., a white girl aged 6, was referred for a dermatologic consultation from the Department of Pediatrics, University of Illinois Research and Educational Hospital. Five months previously a patchy red eruption had developed on the face, beginning in the periorbital region and spreading over the cheeks. Associated with this were muscular weakness and fatigability, but no other constitutional signs or symptoms. A diagnosis of lupus erythematosus was made and liver extract and injections with bismuth compound were given. However, the muscular weakness increased in severity, and she began to complain of pain and tenderness in the thighs and arms.

The examination revealed a moderately well nourished child, apparently weak and unable to sit up without support. The skin of the periorbital region was edematous, and there was a heliotrope erythema of this and of the butterfly area of the face. Islands of gray-white skin were seen in the erythematous area surrounding the eyelids. Fairly sharply outlined patches of erythema were present on the chin, chest and extensor surfaces of the extremities. There was a bright erythema of the finger tips and a pinkish macular eruption on the palms. Some tenderness and increased firmness of the thigh muscles were noted. The blood and urine were essentially normal.

A muscle biopsy showed interstitial edema and alternate areas of pale-staining and deeper eosinophilic sectors of the muscle fibers. There was atrophy of some of the fibers, of which a few were necrotic or recently regenerated. A heavy perivascular lymphoid infiltration was present. Sufficient skin was not included for adequate study.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I thought that this was a typical case of dermatomyositis with the wasting of the trunk muscles, including the shoulder muscles, and the lupus erythematosus-like eruption on the arms, face and chest, with heliotrope coloring to the eyelids, which latter is characteristic of dermatomyositis. The histologic changes in dermatomyositis are those, however, of toxic dermatitis and show none of the specific changes seen in lupus erythematosus. In dermatomyositis, there usually is no leukopenia or anemia and little change in the sedimentation rate. The reverse is true of disseminate lupus erythematosus. There has been a tendency among some writers in the East to group lupus erythematosus disseminatus and dermatomyositis together, and Libman would even

include scleroderma as well as the previous two diseases under Libman-Sacks disease I believe that this is going too far and that usually one can distinguish one disease from the other, except that the Libman-Sacks original syndrome seemed to be a form of disseminate lupus erythematosus

DR J F MADDEN, St Paul I would like to mention again the use of penicillin in 1 case of early dermatomyositis In that case it was undoubtedly a life-saving measure I think that it should be given a trial in the early stages of the disease

DR JAMES H MITCHELL At the December meeting I showed an early case of dermatomyositis in which extensive penicillin treatment was used The patient died three days after the meeting

DR DAVID V OMENS We have had 3 cases of dermatomyositis in which there was excellent progress with penicillin therapy One boy received 300,000 units a day Two girls, 12 and 13 years old, respectively, improved with penicillin therapy

DR FRANCIS E SENEAR This is the first case of dermatomyositis I have seen with so noticeable a lesion on the lids

A Case for Diagnosis (Congenital Ectodermal Defect?) Presented by DR JAMES R WEBSTER and (by invitation) DR EUGENE T MCENERY

R L, a white infant boy was born Nov 12, 1945, by spontaneous delivery after an uneventful pregnancy He is the only child of his parents At birth two teeth had already erupted, but these have been shed and no others have appeared as yet The child has always had a pale rather dry skin

At birth the nails appeared to be raised from the underlying tissue by accumulations of a clear fluid, but there were no signs of inflammation Fluid was aspirated from under one of them from which *Escherichia coli* was recovered on culture, which observation was felt to be a contamination Soon thereafter this nail was shed, and periodically since that time other nails have so separated from the underlying tissue with little or no subungual keratosis, become convex transversely and then been shed

The infant was born with abundant rather long dark hair, but this was shed early and regrowth of hair on the scalp and eyebrows has been patchy

While still in the hospital the patient had stomatitis, which was treated locally with methylrosaniline chloride along with oral administration of concentrated vitamins B, C and D and finally cleared He also received penicillin by injection, in an attempt to influence the nail changes About one and a half months ago there was a rather sudden swelling of the tongue, which was described as being so large as to interfere somewhat with the taking of food This subsided while penicillin was being used locally and has not recurred

Results of repeated serologic tests on both baby and mother have been negative, and there is no family history of positive serologic reactions or any trouble similar to that presented by the infant The blood has been essentially normal

The examinations reveal a small white infant with a pale dry skin The hair of the scalp and eyebrows is dry, lusterless and somewhat patchy and sparse, although it appears closer to normal than it did a few months ago There is one erupted tooth at present (the infant is 6 months old) The nails of both hands and feet appear somewhat opaque, and some show evidence of separation from their bed by subungual keratosis, with moderate redness of paronychial tissue

Scrapings of the nails, examined after treatment with potassium hydroxide, revealed no fungi. The sections of a shed nail, stained with hematoxylin and eosin after decalcification, showed no noteworthy changes other than some fragmentation, which may or may not be significant.

DISCUSSION

DR THEODORE CORNBLEET: Have a hemoglobin estimation and erythrocyte count been made? Could the administration of iron be of value here? The presence of an ectodermal defect is likely.

DR EDWARD A. OLIVER: These cases have been reported from time to time. Dr. Cole reported one in *The Journal of the American Medical Association* last year, a case that would have been presented at the meeting of the American Medical Association if it had been held. I had the opportunity of writing a discussion for it. All these patients show defects of the hair, teeth and nails. The defects in this one are not quite as prominent as in most. This child shows a dental aplasia, deformity of the nails and scanty hair growth. I was unable to find much evidence of keratosis pilaris, which many of them have. I thoroughly agree with the diagnosis of ectodermal defect of rather mild type. I do not believe that treatment is going to work well. Most of these children do not perspire freely. I questioned the mother, and she said that the child perspired profusely.

DR A. H. SLEPYAN (by invitation): I believe that this child presents the picture of pachyonychia congenita, which belongs to the more comprehensive type known as congenital dyskeratosis (ARCH. DERMAT. & SYPH. 46:317, 1942). Four years ago Dr. Ebert and I presented a 5 year old child with pachyonychia congenita, who showed the other stigmas of this syndrome, namely, the mucous membrane lesions, cheilosis and leukoplakic patches on the buccal mucosa, the follicular keratosis and plugging, resembling verrucae, over the extremities and palms, the bullae over the areas of injury, which were indistinguishable from lesions of epidermolysis bullosa, and, lastly, the nail changes which in our case were minimal, showing but transverse ridging, leukonychia and distal thickening. The patient died suddenly a few months after being presented. At autopsy the only remarkable observation was an enlarged heart, which the pathologists interpreted as a beriberi heart.

DR JAMES R. WEBSTER: The pediatrician reported that the erythrocyte count and hemoglobin have always been within normal limits. When I first saw the child, the weather was cool and the skin was definitely dry. Further, I gained the impression from the mother that there had never been much perspiration. Today it was warm in the examining room and the baby was bathed in perspiration, so that it cannot be said that anhidrosis is part of the picture in this case, although the history and observations definitely place it in the group of congenital ectodermal defects.

DR McENERY has been using fairly concentrated doses of vitamins by mouth and a bland oily medication on the nails. I feel that the general picture is much better today than when I saw the baby about a month ago. However, I realize that the treatment is only palliative.

Lichen Sclerosus et Atrophicus with Involvement of the Vulva Presented by DR L. F. WEBER and DR IRENE NEUHAUSER

DISCUSSION

DR HAMILTON MONTGOMERY, Rochester, Minn.: Lichen sclerosus et atrophicus frequently occurs on the labia in women usually about the time of the menopause and thus may be associated with simple pruritus vulvae, true kraurosis or leuko-

plakic vulvitis. Thus, all four diseases may appear independently. Lichen sclerosus does not cause leukoplakia, and it has been repeatedly confused in gynecologic literature with leukoplakia and kraurosis. In lichen sclerosus et atrophicus, the process also extends to involve the skin around the anus, so that there is a perianal ring which is distinctive.

DR S W BECKER. I think that one of the reasons for confusion is that gynecologists are not dermatologists and they call most lesions about the vulva "kraurosis vulvae." I have seen psoriasis of the vulva called kraurosis, and I have seen localized neurodermatitis called kraurosis. I had occasion to look over a number of slides for a gynecologist in a case in which he had made a diagnosis of kraurosis vulvae. Many of the slides were typical of lichen sclerosus et atrophicus microscopically. Some showed leukoplakia. At least in the gynecologic literature one must be careful about accepting the diagnosis of kraurosis, because it includes several entities.

DR H E MICHELSON, Minneapolis. One of the unfortunate things about this condition is that it is described as a lichenoid disease. It is too bad that teachers do not emphasize that it is almost always a plaque disease. For my own part, I have seen few patients with guttate morphea.

A Case for Diagnosis (Epithelioma of the Glans Penis?) Presented by
DR FRANCIS E SENEAR and STAFF

Marcus R Caro, MD, *President*

Leonard F Weber, MD, *Secretary*

Oct 16, 1946

A Case for Diagnosis Tuberculosis Cutis? Extensive Ulceration of Chest Wall, Neck and Ear Presented by DR M H EBERT and (by invitation) DR J GRAFFIN

A Case for Diagnosis (Lupus Vulgaris?) Presented by DR T CORNBLEET and (by invitation) DR H SHORR and DR N L BAKER

The patient presented is an 11 year old Negro boy, A S, whose mother first noticed reddish yellow crusts obstructing the nares seven months ago. Four months ago, a pea-sized granulomatous tumor appeared on the right side of the upper lip.

There is a crusted granulomatous enlargement of the distal half of the nose and in the nares similar granulomas, causing almost complete obstruction of the airway. On the right side of the upper lip there is a granulomatous mass 2.5 cm in diameter, which is friable and bleeds easily. On the soft palate there are four translucent masses 5 mm in diameter.

The result of the Mantoux test was strongly positive. The urine was normal. The Kahn reaction of the blood was negative. There was a normal hemogram. The roentgenograms of the hands and feet were normal, the roentgenogram of the chest showed a large calcified paratracheal lymph node. Cultures on Sabouraud's medium were negative for fungi. Stomach washings were negative for tubercle bacilli.

DISCUSSION

DR EDWARD A OLIVER. This case is similar in many respects to one in Ormsby's textbook of a young Italian with lupus vulgaris. I realize that in the

present case the microscopic picture is not that of lupus vulgaris I would suggest the taking of another biopsy specimen from a more suitable place.

DR HERBERT RATTNER The British have been writing enthusiastically about the use of large doses of calciferol (vitamin D₂), 200 mg a day, for cutaneous tuberculosis They report striking improvement even in cases of extensive disease in two or three months

DR H E. MICHELSON My colleagues and I became intensely interested in the Charpy treatment (vitamin D₂) when we read about it in the foreign literature and have used the method in about 12 cases Our results are not as striking as those in the French and British report, but that may be due to the fact that the base line of nutrition is so different here The important ingredient of the Charpy treatment is vitamin D₂ and I do not believe that it is so important that it be administered in alcoholic solution, although Charpy recommended that

DR IRENE NEUHAUSER I recently visited the Children's Hospital in Mexico City, where they were using the Charpy treatment Their results are incredible Some of the children had Pott's disease and scrofuloderma associated with cutaneous lesions With the Charpy treatment the lesions were completely cleared up in two or three months

DR THEODORE CORNBLEET For a group of patients with lupus vulgaris and other forms of tuberculosis of the skin, my co-workers and I have been employing vitamin D in various forms and in different regimens We are able to corroborate the good results obtained by Charpy and by Dowling and Thomas with the use of vitamin D We feel, on the basis of actual trial and comparison, that other forms of vitamin D do not give the good results that follow the use of vitamin D₂ or calciferol It must be remembered that commercial vitamin D made from ergosterol by ultraviolet irradiation or electrical discharges contains spectrums of various vitamin D composition It is possible that all these artificial products as well as naturally occurring vitamin D in fish liver oils, improve cutaneous tuberculosis, because they contain the D₂ form among others It may eventually be found that vitamin D₂ or calciferol, is the only effective form We have seen good results when the dosage forms and regimen advocated by Charpy have been altered We did not find, as he did, that it is necessary for the vitamin D₂ to be administered in alcohol We have not found the concomitant use of calcium in the form of milk or otherwise to be mandatory for obtaining improvement in our patients We have not seen untoward results with a dosage of 100,000 units daily for an extended period

Boeck's Sarcoidosis (with Active Pulmonary Tuberculosis) Presented by DR. D OMENS and (by invitation) DRS H OMENS and J GRAFFIN

DISCUSSION

DR H E MICHELSON, Minneapolis I like the term "sarcoidosis" and believe it would be well to drop such terms as Boeck's disease and Schaumann's disease. I wonder whether if in a case such as this one dares make a diagnosis of sarcoidosis in the face of frank tuberculosis I also bring up the question of whether one can diagnose sarcoidosis in microscopic examination I believe that we have been all too willing to make such a diagnosis, and I think that one must be very careful in interpreting the microscopic section

DR M H EBERT Dr Nomland had some cases which illustrated the fact that in Negro patients with sarcoidosis the immunity or reactivity could unfortu-

nately be changed and a positive tuberculin reaction and open tuberculous lesions could develop. Again the disease may change and reverse itself, the tuberculin reaction again becoming negative, and no bacilli can be demonstrated anywhere—the disease runs a benign course for some time. This not only occurs in Negro patients but also in white patients. I think that what is found at the time of examination depends on the phase of the disease. It is not unbelievable that the disease in this patient is in a changing phase. He has sarcoidosis. His disease is changing, and open tuberculosis now developing. Very shortly there will be a positive tuberculin reaction and he will have tuberculosis as well as sarcoidosis in the skin.

DR RUBEN NOMLAND, Iowa City. I was not sure whether this man had sarcoid as it is seen in the Negro. The elementary lesions, seen individually, were a great deal like those of papular sarcoid and the microscopic appearance was compatible with sarcoid. The distribution was a little different from that in sarcoid, only a few lesions were on the face and one or two on the eyelids. The eruption was compatible with sarcoid, but I am not sure about what relation it had to open tuberculosis with positive sputum. I am not sure that I have seen positive sputum develop in Negroes with a sarcoid eruption. I have observed the development of lesions in the lungs of patients with sarcoid, but I think that the development of tuberculosis is rather rare. If tuberculosis does develop with sarcoid, it does not necessarily prove that the sarcoid has anything to do with tuberculosis, because tuberculosis is extremely common in the Negro. I am not at all convinced that sarcoid can be said to have been caused by the tuberculosis, though it is probably tuberculous.

DR MAURICE OPPENHEIM (by invitation). Some of the lesions in this case looked like tuberculosis papulonecrotica, and some like so-called sarcoidosis. Kyrle has found that active tubercle bacilli cause an acute lymphocytic reaction, and the less virulent they are the more they produce tuberculoid structures. It may be that in this case there is a tuberculoid or lupoid reaction in the form of sarcoidosis. I do not believe that sarcoidosis is present in a patient with active tuberculosis. There is now a cutaneous test for sarcoidosis, the Kweim test, reported from the Danholt Clinic in Oslo, Norway, with an antigen which forms papules and nodules in about two or three months. It might be well to perform this test in this case.

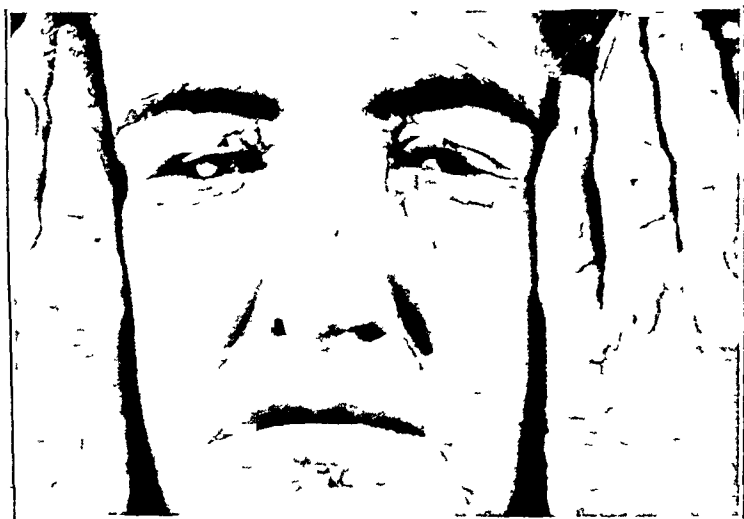
Pyoderma Facialis Presented by DR D OMENS and (by invitation) DR H OMENS and DR N L BAKER

Unusually Extensive Xanthomatosis Presented by DR H RATTNER and (by invitation) DR H RODIN and DR J GRAFFIN

Mrs F W, a 39 year old Jewess born in Russia, in 1942 first noticed yellowish nodules on the skin over the tendon of achilles. Several months later, similar nodules appeared on the flexural creases of the palms. In the past four years lesions have appeared successively also on the face, cornea, elbows, knees, trunk and toes.

From September, 1944 until August 1945 she was confined to a hospital because of severe jaundice. She entered Cook County Hospital one year later because of persistence of the jaundice. At that time the lesions that are present today were noted—yellowish red nodules of the skin over the achilles tendon, the flexural creases of the palms, the cornea, toes, elbows and knees and a few on the trunk.

On the skin of the upper part of the chest there is an area with yellowish mottling with a sort of crepe-paper-like texture with a few pea-sized yellowish red nodules. The liver edge is palpable, but not the spleen. The blood pressure is 120 systolic and 80 diastolic, and a systolic murmur is heard over the entire precordium. The Kahn reaction of the blood was negative. The urine and stool analysis showed no abnormalities. The roentgenograms of the chest and skull were normal. Examination of the blood showed hemoglobin 54 per cent, erythrocytes 3,670,000, and leukocytes 3,900, with 75 per cent neutrophils. The icterus index averaged 61 units. The total cholesterol was 1,300 mg per hundred cubic centimeters (150 to 250 mg). Cholesterol esters were 15 per cent of the total cholesterol content (50 to 75 mg). The total lipids were 501 Gm per hundred cubic centimeters of serum. The total protein was 6.82 Gm per hundred cubic centimeters, with albumin 3.2 Gm and globulin 3.6 Gm. The alkaline phosphatase was 57.9 units (15 to 40). The prothrombin was 75 per cent. The Takata-Ara and cephalin flocculation tests of the liver indicated severe hepatic dysfunction. A biopsy of the



Patient with extensive xanthomatosis

liver revealed moderate fatty infiltration, inequality of hepatic cell size, degeneration and perilymphangitis. The basal metabolic rate was plus 38 per cent. The electrocardiogram was essentially normal.

DISCUSSION

DR CARL W. LAYMON, Minneapolis. This patient presents an unusual number of lesions. Because of their size and the fact that the extensor surfaces are more intensely involved, I should classify the disease as one of the tuberous type. I have never encountered a case of xanthomatosis in which the blood cholesterol was as high as 1,300 mg per hundred cubic centimeters. It has been pointed out by several observers that there is apt to be involvement of the liver when xanthomatous lesions occur on the palms and soles. Such an occurrence was well exemplified in this case. The involvement of the cornea was also most unusual. Another interesting feature was the involvement of the chest and shoulders which simulated pseudo xanthoma elasticum.

DR THEODORE CORNBLEET. The distorted esters ratio reflects somewhat the jaundice that is present. In the group of patients at Cook County Hospital with

jaundice whom my co-workers and I have been studying, our studies have been concerned with the differential observations in the presence and absence of pruritus. Thus far we have found no differences. At the same time we have attempted to make use of the newer knowledge in the nutritional functioning of the liver. It has seemed to us that choline, cystine and methionine may be helpful at times.

Dermatomyositis (Second Attack) Presented by DR. M. H. EBERT and (by invitation) DR. N. BAKER

The patient, a 16 year old white boy, H. K., spent four and a half months in the Cook County Hospital in 1944 because of weakness and edema of the face and extremities. He received 1,000,000 units of penicillin intramuscularly in one month, after which he was able to leave the hospital, apparently recovered. He led a normal active life until six weeks ago, when weakness and low backache appeared. A month ago, his eyelids became edematous, and erythema of the mandibular areas, eyelids and knuckles occurred. Since then, weakness has become severe, being especially pronounced in the thighs, arms and forearms.

Examination shows an adequately developed and nourished white boy. There is erythema of the eyelids bilaterally and edema of the eyelids and cheeks. He is able to rise to the sitting position by pushing on the bed with his hands. Gross weakness of the abductors of the thighs, the anterior muscles of the neck and the extensors of the legs is found.

The leukocytes were 12,800 with a normal differential count, the erythrocytes 4,250,000 and hemoglobin 14.5 Gm. The roentgenogram of the chest was normal. Total serum protein was 5.2 Gm., serum calcium 8.8 mg., phosphorus 4.5 mg. and alkaline phosphatase (Bodansky), 3.4 mg. per hundred cubic centimeters.

He now receives 10 grains (650 mg.) of sulfadiazine every four hours and 100,000 units of penicillin intramuscularly every three hours.

A biopsy specimen was taken from the pectoralis major muscle in 1944. An examination of the sections revealed decided degenerative changes in the muscle fibers, with an infiltration of lymphocytes between the fibers and lymphocytes with a few polymorphonuclear leukocytes in the perimysium. Some of the fibers showed vacuolar and granular degeneration. Some were fragmented and shrunken, with disappearance of the transverse striae. There were no significant changes in the blood vessels, although in places the round cell infiltrate was perivascular.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn. It is remarkable to see such a complete degree of remission in dermatomyositis which occurred in childhood. Usually the course is unfavorable, and during puberty there may arise symptoms similar to the Cushing syndrome, and there may be ankylosis of joints as well as calcification of the skin and a severe degree of disability.

Lupus Erythematosus Disseminatus in a 43 Year Old Full Blooded American Negro Man Presented by DR. M. H. EBERT and (by invitation) DR. J. GRAFFIN

Acute Disseminated Lupus Erythematosus Successfully Treated with Penicillin Presented by DR. JAMES H. MITCHELL and (by invitation) DR. ROBERT GOODWIN

DISCUSSION

DR. A. L. WELSH, Cincinnati I think that it has been interesting to note that some of the patients with acute disseminated lupus erythematosus will respond to massive doses of penicillin. On the other hand, my co-workers and I have had some patients who showed practically no benefit from the use of penicillin. In patients in whom a response was produced with penicillin, relapses have been rather common. In two such instances when penicillin was again used, there was no benefit. It appears that massive doses (such as 1,000,000 units every three hours) are required for adequate response in at least some of these patients. The Indian patient had an episode of illness, at an earlier date, which was not explained and from which he recovered. We have had 6 patients in the last two years with acute disseminated lupus erythematosus, who had had previous illnesses associated with fatigue, muscle pains and a nondescript picture which could not be classified. They apparently recovered. Later, they reappeared on the medical service with lupus erythematosus of the acute disseminated type. It is strange that the cutaneous lesions of lupus erythematosus, which are so typical, both clinically and histologically, appear and disappear in the course of the disease. We have all seen the skin of patients with disseminated lupus erythematosus clear completely, and the patients then die of the disease. We have had 2 such cases in the last two years.

DR. STEPHEN ROTHMAN It is too early yet to say anything definite about penicillin therapy of acute lupus erythematosus. It seems that the routine dose of 30,000 to 40,000 units every three hours has no effect on the process. So far my co-workers and I treated 4 patients with considerably higher doses. One of them, a woman 61 years old, was shown here several months ago. She was desperately ill, but has now been free from signs and symptoms for four months. She was given 8,000,000 units of penicillin daily on three consecutive days, and this course was repeated after a two week interval. A 14 year old girl was brought to the hospital with acutely exacerbated lupus erythematosus. She is well today, after having been given similarly huge doses of penicillin and castration had been performed. In each case these huge doses caused a transitory therapeutic reaction with exacerbation of fever, flare-up of the eruption and fall in white cell count. Improvement set in three to four days after the administration of penicillin was discontinued.

NOTE—As of May 18, 1947, 2 of the 4 patients had died. The 2 living patients, an aged woman and a child, had been well for one year and for six months, respectively.

DR. D. V. OMENS I have had a patient in the hospital who had a stormy course of lupus erythematosus. She is undergoing the second involution period of lupus erythematosus and has had no penicillin.

DR. RICHARD S. WEISS, St. Louis I have been asked about the use of folic acid in the treatment of disseminated lupus erythematosus. I have now treated 3 patients with it. In the first case there was a very limited supply, and the patient received only ten doses, at the end of ten months, with supportive treatment, she seemed to have completely recovered. When last seen, four months ago, she was still apparently well.

The second case was of the subacute disseminated form. The patient received daily injections of 10 mg. folic acid, and she began to improve materially and was discharged from the hospital in four weeks. Folic acid therapy was followed by treatment with crude liver extract, and the patient's improved condition has been maintained.

The third patient was given the drug about four or five weeks ago. This was another case of the disseminated subacute type. Her general symptoms have now disappeared, and her skin shows definite improvement.

I do not make any claim that this is a cure for lupus erythematosus. The patients were given the benefit of rest and high caloric feeding, and a remission occurred during this treatment. I am reporting these cases now so that others may try the effect of folic acid.

DR STEPHAN EPSTEIN, Marshfield, Wis. One point I would like to mention. There should be differentiation between acute lupus erythematosus and the cases of subacute disease frequently presented as acute lupus erythematosus. I believe that this case represents the subacute form with remission following folic acid therapy, such as is seen after treatment with niacinamide and liver extract. I wonder whether penicillin has been tried in the cases of fulminating lupus erythematosus.

DR M. H. EBERT. There are to be noted one or two features about the Indian patient. In our clinics few American Indians are seen. This is the first one I have seen with lupus erythematosus. The disseminated variety in male patients is rare, but it does occur and is frequently fatal. The most interesting point, however, is the prolonged history of arthritic muscular weakness for fourteen years. As Dr. Welch pointed out, it may have been lupus erythematosus all the time, of the disseminated variety without cutaneous manifestations. However, he has been in the hospital a very short time, not long enough to have obtained the biopsy report, but I am sure that there will be characteristic observations. I think that he should have a neurologic examination. There may be some other explanation for this weakness. Clinically one would think that this was a case of disseminated discoid lupus erythematosus, but actually the patient has the systemic manifestations of the other variety.

Hodgkin's Disease of the Skin. Ulcerated Nodules. Presented by DR. H. RATTNER and (by invitation) DR. H. RODIN and DR. J. GRAFFIN.

Paraffinoma of the Buttocks and Back. Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. J. GRAFFIN.

W. M., a 71 year old white man, noticed nodules in his buttocks for the first time about thirty years ago. At the time he was receiving injections of mercury daily in the buttocks for syphilis. However, he does not remember having received injections in the lower posterior thoracic region. These nodules have never ulcerated and have persisted as hard masses until the present time. He also received a course of nearsphenamine in addition. About ten years ago his right knee became swollen and prevented him from walking without support. Five years ago the left knee became swollen causing him to be practically bedridden since that time.

He entered a neurologic ward at Cook County Hospital in 1946, at which time a clinical diagnosis of Charcot's joints, tabes dorsalis and trophic ulcers of the feet was made. Involving almost the entire buttocks of both sides is a hard nodular sharply defined mass in the subcutaneous tissue. The overlying skin is bound down to this mass and is bluish red. The intervening skin and subcutaneous tissue between the masses are essentially normal. There are two similar masses about 15 by 7 cm in both lower posterior thoracic regions. There is a systolic murmur over the apex and a diastolic one over the aortic area, with a blood pressure of 132 systolic and 84 diastolic.

The Kahn reactions of the blood and spinal fluid were negative. The urine, blood picture and roentgenogram of the chest were essentially normal. The roentgenogram of both knees showed changes compatible with a diagnosis of Charcot's joints. The electrocardiogram showed evidence of myocardial damage. The histologic section from a lesion in the buttocks showed a densely packed mass of degenerated pale fibers separated by many clear spaces. The sudan III stain showed the clear spaces to contain droplets of the brightly stained fat. The fibers were also stained by sudan III, but stain here was more pale and granular. The polariscopic examination failed to show any double refraction.

DISCUSSION

DR RICHARD S. WEISS, St. Louis. This is an extraordinary manifestation of paraffinoma. All of us remember the cases that Mook originally described which were due to the injection of camphor liniment. From this man's history one must assume that he received injections of mercury in oil, probably mineral oil. I have never seen paraffinomas develop from the thousands of injections of mercury salicylate and mineral oil that were given in the treatment of syphilis many years ago. This patient stated that he received the injections only in the buttocks, but he must have had some in the back as he has these lesions in the scapular and subscapular regions. Lesions appeared to be produced by the burrowing of the oil along the fascial planes, thus producing, in distant areas, granulomas enclosing oil cysts. Sections from this patient showed some evidence of oil cysts, but most of the reaction was fibrous. I certainly am inclined to think that the diagnosis given is correct, but this is the first case I have seen that has apparently followed injections of a mercurial preparation in oil.

DR STEPHEN ROTHMAN. It is my understanding that injections of vegetable oils do not cause development of paraffinomas. Injection of mineral oils, of course, is not permissible, because they are not absorbed and invariably cause foreign body reactions. I wonder whether this man received injections of mercury salicylate which was suspended in paraffin oil.

DR S. J. ZAKON. This brings up a question regarding the use of penicillin in wax. Dr. Jones of the department of pharmacology stated that the use of wax intramuscularly is bound to result in lesions similar to paraffinoma.

DR S. W. BECKER. Dr. O'Leary may remember a patient at the Mayo Clinic in 1925 who contracted syphilis at the time of the World's Fair in 1893. He had been treated with some mercury compound and his buttocks resembled those of this patient. He had an enormous tumor on each buttock, but there was nothing on the trunk. I questioned the patient carefully about injections in the back, and he said that he had not received any. He had received his treatment in 1911, and he may have forgotten at which sites injections were made. I think that these tumors are paraffinomas resulting, perhaps, from the administration of the drug in some insoluble oil, such as mineral oil.

DR THEODORE CORNBLEET. It would seem improbable to me that this man received injections at all the sites that are now involved. I agree that the original paraffin lakes could be distributed downward, as by gravity. On the other hand, the depots could have been disseminated upward along fascial planes, propelled by the action of various muscle groups. One reason for showing this patient is to demonstrate the fluorescence of the paraffin lakes in the tissue sections. I could not complete the arrangement for demonstrating the diagnostic purplish blue by means of the fluorescent microscope. This is the method Dr. Popper and I described several years ago (*ARCH. DERMAT. & SYPH.* 47: 637 [May] 1943).

Pterygium Colli (Bonevie-Ulrich Syndrome) Presented by DR D OMENS and (by invitation) DR H D OMENS and DR N L BAKER

The patient, a 3 week old white baby girl, was delivered by cesarean section at full term, of a 23 year old primiparous mother. The baby appears mongoloid, with long narrow epicanthal folds, the skull is microcephalic. There is a great redundancy of skin from the nuchal ridge to the interscapular area. At the left posterior portion of the neck there is a subcutaneous flabby cyst with fluid contents. The ears have no tragus. The tongue is grossly enlarged and hard. The lips are enlarged and indurated. There is pitting edema of the hands, feet and legs. The fingers are thickened at the base, and they taper. The finger nails are very small. The palms and soles are bright red. The palmar and plantar areas are sharply demarcated from the upper portion and the soles by a ridge encircling the foot.

Roentgenograms of the spine, forearms and legs showed no osseous pathologic condition. The femoral epiphyses were well formed. The roentgenograms of the skull were normal. Serum calcium was 10.7 mg per hundred cubic centimeters. The Kahn reaction of the blood was negative. The hemogram was normal.

Thyroid, $\frac{1}{4}$ grain (16 mg) per day, was given, but treatment was discontinued when fever occurred. The temperature ranges from 95 to 98.6 F rectally.

DISCUSSION

DR DAVID V OMENS: About 25 cases of this condition have been reported from Switzerland and France. It has been suggested that the cause may be a lack of iodine. The symptoms are mental retardation, macroglossia, edema of the hands and feet because of lymph stasis, tiny ears, cholesteremia, redundant skin in the axillas, inguinal region or neck, dystrophy of nails, and osteoporosis. Later mushrooming of the femoral epiphysis and digital compression of the skull are seen on roentgenographic examination.

A Case for Diagnosis (Erythema Figurata Perstans?) Presented by DR F E SENEAR and STAFF**Regrowth of Hair After a Second Epilation for Tinea Capitis** Presented by DR JAMES H MITCHELL and (by invitation) DR ROBERT GOODWIN

W P, a boy now 12 years old, was first seen in April 1945, because of patchy alopecia of six months' duration. He had typical "gray patch" ringworm of the scalp, confirmed under the Wood light and by culturing *Microsporon audouinii* from affected hairs.

On May 11 epilation by the five point method (350 r to each of five areas) was done, defluvium of hair being nearly complete by June 1. By June 22 it was apparent that a dollar-sized area of fluorescent hairs over the occiput was not affected by the roentgen rays. Despite concentrated treatment with various ointments (ammoniated mercury, benzoic and salicylic acid ointments, iodine in goose grease, salicylanilide, and undecylenic acid with zinc undecylinate) and manual epilation to toleration, this focus persisted.

On May 17, 1946, reepilation was done with the identical technic used previously, with the same consequence—a persistent area over the occiput unaffected by the roentgen rays.

Treatment with iodine in goose grease, to provoke a kerion, and manual epilation have resulted in little improvement.

Normal regrowth of hair following the second epilation was well established by September 6 (sixteen weeks after roentgen treatment).

Tinea Capitis in a Woman Aged 46, Mother of Two Children with Tinea Capitis (*Microsporon Audouini* Type) Presented by DR. I. M. FELSHER and DR. CLARK W. FINNERUD

DISCUSSION

DR. STEPHEN ROTHMAN *Microsporon audouini* infection of the scalp in the adult is exceptional. So far as I have found, only 2 cases have been reported in which the cultural diagnosis was beyond doubt. The absence of immunity on the scalp of adults may have two explanations. One is deficiency in sex hormones with incomplete development of sebaceous glands, and the other is an individual variation in the chemical composition of sebum with fungicidal fatty acids below the critical concentration (Rothman, S.; Smiljanic, A.; Shapiro, A. L., and Weitkamp, A. W. Spontaneous Cure of Tinea Capitis in Puberty, *J. Invest. Dermat.* 8:81-98 [Feb.] 1947). This woman obviously is not suffering from hypogonadism, though her menstrual flow has been conspicuously weak in the last few years. However, she stated that all her life her hair had been extremely dry. She never felt the need of washing it, a sign of deficient sebaceous gland secretion.

DR. I. M. FELSHER The woman desires roentgen treatment for herself. I have not had the experience of treating a woman of that age by roentgen epilation. Besides, she has chronic bronchitis with bronchiectasis and severe secondary anemia, with severe episodes, one confining her to bed for two months with an elevated temperature of 100 to 103 F. Would it be safe to proceed with roentgen treatment in her case, or is it better to treat her with topical applications?

On a number of occasions the problem of administering a second dose of roentgen rays for epilation was presented. If the epilation was incomplete from the first dose, I usually allowed a period of six months to elapse before giving a second epilating dose of roentgen rays and have had no difficulty with the regrowth of hair.

Dr. Fox's survey, which goes back to 1928, is the best we have regarding the rarity of *M. audouini* in the adult. He found about 70 cases of tinea capitis of the scalp in adults. Fifty-one of these cases were proved by microscopic examination or culture. Of these, in 6 or 8 cases he found *M. audouini*. He also reported a case of infection with *M. audouini* in an adult causing kerion. Mendelsohn also reported a case of tinea capitis in an adult caused by *M. audouini*. Dr. Fox also found that in Japan the preponderance of tinea capitis in the adult was much greater. In the United States there were only 7 cases, and they occurred predominately in the female sex. In Japan the reverse was true, the male sex was affected in a larger number of instances.

DR. JAMES H. MITCHELL I had a patient, a woman, with favus in the clinic for a number of years. Epilation was done, but the favus went on blooming after epilation.

Turban Tumors (Nevus Epitheliomata-Cylindromatosus plus Sebaceous Cysts) in a Man Aged 68 Years Presented by DR. E. A. OLIVER and DR. H. RALLNER.

A Case for Diagnosis (Eosinophilic Leukemia?) Presented by DR. E. A. OLIVER, DR. J. R. WEBSER, DR. J. E. GINSBERG and DR. H. S. STEINBERG.

A white man aged 26, from the Hines Veterans Hospital, stated that his cutaneous disease began in December 1945. He first noted several papules, with pinhead-sized crusts on his chest, upper part of the abdomen and shoulders. These

were associated with severe pruritus. Topical treatment failed to affect improvement. When he entered the hospital in June 1946, examination revealed an acutely ill white man complaining of general weakness and a generalized pustular pruritic eruption. The skin showed numerous impetiginous, honey-colored, crusted lesions on the face, chin and neck, and numerous pea-sized pustular, umbilicated and crusted lesions on the neck, posterolateral aspect of the shoulders and on the hands and feet. On the trunk and extremities, especially the upper part of the thighs and inguinal regions, there were large areas of depigmented skin, the site of previous lesions. There were pustules and bullae on his feet, his ankles were swollen, and there were numerous pustules on his scalp. He had a temperature of 100 to 101 F each evening, with occasional spikes to 103 or 104 F. Blood cultures were sterile.

Laboratory observations on admission were as follows. The urine was normal. Examination of the blood showed erythrocytes 3,500,000, hemoglobin 11 Gm and leukocytes 15,800, with polymorphonuclear cells 64 per cent, lymphocytes 23 and eosinophils 13. Wassermann and Kahn reactions of the blood were negative. Nonprotein nitrogen was 30 mg, creatinin 1.3 mg, blood sugar 93 mg and total protein 6.9 Gm (albumin 3.4 and globulin 3.5). The roentgenogram of the chest was normal. Results of routine polyagglutinations for typhoid and paratyphoid were negative. Despite energetic treatment, his general condition remained unchanged, but new vesicular and bullous lesions continued to develop. The hands became edematous, the feet and legs were the seat of numerous vesicopustules, many of which fused to form confluent patches.

The blood was studied carefully in July, August, September and October and revealed the changes shown in the table.

Results of Studies of the Blood

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Poly morpho nuclear Cells	Lymphocytes	Eosinophils
July 1	4,470,000	85	20,200	52	41	7
July 15	4,470,000	85	34,000	42	10	28
August 5	4,630,000	90	39,000	16	21	63
August 7	4,860,000	95	56,000	20	33	47
August 29	5,150,000	100	39,600	15	45	40
August 31	5,000,000	95	21,800	63	20	17
September 10	5,130,000	100	26,000	41	47	11
October 8	4,790,000	90	15,200	51	38	11

About August 5, the patient complained of a slight cough, the physical examination revealed only slightly exaggerated breath sounds. Results of sputum examinations were negative for fungi and tubercle bacilli, but roentgenograms of the chest revealed soft shadows of increased density in both lung fields. On August 22, another roentgenogram was taken, and this indicated almost complete disappearance of the infiltration. The roentgenologist expressed the belief that this corresponded to the syndrome described by Loeffler in 1932, a syndrome characterized by transitory pulmonary lesions, decided eosinophilia and a mild clinical course, in contrast to extensive pulmonary changes seen in the roentgenogram. Sternal puncture did not reveal any evidence of leukemia. The bone marrow was reported as hyperplastic and contained all the normal elements.

A section taken from the skin and stained with hematoxylin and eosin showed slight acanthosis and edema of the epidermis, with patchy parakeratosis. In one region there was an extensive crust composed of fibrin containing many

polymorphonuclear and round cells. In the corium there was moderate edema, superficial vascular dilatation and a diffuse cell infiltrate in the upper third, rather sharply limited below, except that it extended more deeply in the regions of the epidermal appendages. In the papillae themselves, the infiltrate was rather sparse, but in the subpapillary region, it was dense and closely packed. This infiltrate was composed of round cells and many eosinophils. The round cells exhibited definite, though not pronounced, variation in size and staining qualities. There were some pyknosis and karyorrhexis.

DISCUSSION

DR PAUL O'LEARY, Rochester, Minn. I suggest the diagnosis of eosinophilic leukemia, which is not eosinophilic granuloma. At the Mayo Clinic we recently dismissed a patient who presented the same clinical and hematologic picture presented in Dr. Oliver's case. The disease starts as an acute vesicular eruption, characterized by periods of severe pruritus, followed by the appearance of erythema-multiforme-like lesions with showers of vesicles. The subsequent course has been a recurrence of the vesicular type of eruption, sometimes small vesicles and rarely bullae, covering the greater part of the body. Increased pigmentation was pronounced in our patient. The blood picture is interesting and is of differential value in distinguishing the disease from dermatitis herpetiformis and erythema multiforme. An eosinophil count of 50 to 55 per cent with a leukocyte count of about 40,000 persisted for several months. A sternal puncture did not offer additional information. The term eosinophilic leukemia means something different than eosinophilic granuloma, I do not believe that this patient has eosinophilic granuloma. We adopted the term eosinophilic leukemia because the hematologists had no explanation to offer for the observations of the blood, because morphologically the patient had a severe degree of pseudo-dermatitis-herpetiformis-like eruption and because the blood cell counts slowly returned to normal and the cutaneous lesions disappeared after high voltage roentgen therapy.

DR STEPHAN EPSTEIN, Marshfield, Wis. Eosinophilic granuloma of the bone closely resembles Schuller-Christian's disease. I do not know whether eosinophilic leukemia is at all related to eosinophilic granuloma of the bone. The type of cutaneous lesion presented here has not been described in studies of eosinophilic granuloma of the bone.

DR ADOLPH ROSTENBERG JR (by invitation). I do not know what this man has, but it seems to me that we are overlooking one approach that might be of some help in diagnosis. There is a history of Loeffler's syndrome in this patient. Loeffler's syndrome is being recognized with increasing frequency. Several cases have been reported in association with creeping eruption. It is looked on as a sensitization phenomenon, sometimes to some organism, such as intestinal or cutaneous parasites. The cutaneous lesions this man shows might be an expression of such a sensitization.

DR EDWARD A. OLIVER. When this man first entered Hines Hospital he was very sick. He was pale, weak and cachectic and had a fever. The eruption was a generalized one, occupying the face, trunk, arms, legs and back, with a great deal of eruption in the groins and on the inner aspects of the thighs. The lesions were vesicles, papulovesicles and small bullae. Our first diagnosis was dermatitis herpetiformis. Several weeks later the cutaneous picture changed, we then changed our diagnosis to pemphigus. He has had a great deal of treatment, including treatment with acetarsone, penicillin and streptomycin, and

he has improved a great deal. At one time in the course of the disease a typical Loeffler syndrome developed. I am especially indebted to Dr O'Leary for his remarks, we shall try to follow out the treatment as suggested by him

Chancere, on the Cheek Presented by DR E A OLIVER, DR J E GINSBERG, DR J R WEBSTER and (by invitation) DR H S STEINBERG

A Case for Diagnosis (Lymphangioma Circumscriptum?) Presented by DR E A OLIVER, DR J E GINSBERG, DR J R WEBSTER and (by invitation) DR H S STEINBERG

A Case for Diagnosis (Drug Eruption?) Presented by DR S ROTHMAN and (by invitation) DR H F KRYSA

Psoriasis with Hyperkeratosis of Palms and Soles (Arsenical?) Presented by DR F E SENEAR and STAFF

Pustular Psoriasis? Acrodermatitis Continua? Presented by DR S ROTHMAN and (by invitation) DR E L LADEN

A Case for Diagnosis Pustular Eruption of the Fingers and Toe Presented by DR STEPHAN EPSTEIN, Marshfield, Wis

Necrobiosis Lipoidica Diabeticorum Presented by DR H RATTNER and (by invitation) DR I EIRINBERG

Adenoma Sebaceum? Presented by DR CLEVELAND J WHITE

DISCUSSION

DR HENRY A BRUNSTING, Toledo, Ohio (by invitation) This disorder would be better classified as a syndrome rather than a distinct entity. In reviewing the literature on this subject, it is necessary to consult articles written by the neurologists, urologists, cardiologists and various other specialists, for each one reports that phase of the syndrome in which he is most interested and any involvement of the skin may be mentioned briefly or omitted. The disorder is essentially a congenital ectodermal defect. Various degrees of mental retardation may be present, and roentgen examination of the head is indicated. One may encounter associated tumors of the retina, heart, kidney and other structures, and therefore each patient should receive the benefit of a thorough general physical examination.

DR MAURICE OPPENHEIM (by invitation) I consider adenoma sebaceum to be a forme fruste of von Recklinghausen's disease. On the back of this patient there are fibroma molluscum and deep pigmentations, a form of von Recklinghausen's disease. There is a possibility that adenoma sebaceum is only an abortive form of this disease. I do not know whether the sella turcica was enlarged, roentgenographic examination should be made, because often an enlargement of the sella turcica is found.

Congenital Amniotic Constriction Rings Presented by DR F E SENEAR and STAFF

D T, a 22 month old infant, was seen in the Department of Orthopedics, University of Illinois Research and Educational Hospitals. Abnormalities in

the skin of the extremities had been present since birth. There was a firm depressed scar completely encircling the left thigh in its lower third. No edema or circulatory changes were apparent distal to the scar. Similar lesions on the leg, upper part of the thigh and arms had been surgically corrected by Z-plasty. There was a talipes equinovarus deformity of the right foot.

Results of routine laboratory studies revealed no abnormalities. Biopsy (of previously operated lesion) revealed an intact relatively normal epidermis. The corium showed dense interwoven bands of connective tissue associated with prominent blood vessels and foreign body reaction, presumably above keratin deposits but with a total absence of cutaneous appendages.

Blastomycosis (Gilchrist) Presented by DR S ROTHMAN and (by invitation) DR J H MCCREARY

W L, a 52 year old man, a railroad clerk, was well all his life until he squeezed a boil on his left arm in September 1938. The lesion enlarged and spread gradually. Blastomycosis was diagnosed in 1939. Treatment up to the time of admission, May 5, 1946, in Billings Hospital, consisted of a series of roentgen ray treatments, local applications of sulfur and copper sulfate, administration of iodides, penicillin and iron.

On admission, the patient was emaciated, weak and unable to move. He had lost much weight. There was no fever and no pain. The skin of the face, hands, forearms, left thigh, buttocks, perianal area and abdomen were involved in a deep ulcerative process. The ulcerative plaques were surrounded by an infiltrated and hyperkeratotic border in arciform and polycyclic patterns, studded with milium abscesses. The destructive process had continued in the left forearm and hand down to the superficial muscle tendons. The cartilaginous part of the nose had been destroyed. Contractile scarring had produced flexural contractures of the arms and left hand and ectropion of the right eye. There was sufficient tissue destruction in the perianal area to interfere with sphincter control. A decubitus ulcer was present in the sacral region.

There have been no physical signs of involvement of the chest, but roentgenograms of the chest showed diffuse fibrosis compatible with blastomycosis. A roentgenogram of the left hand showed generalized osteoporosis. The urine was normal. There was slight leukocytosis (11,000 to 12,000 white blood cells). The differential count was normal. Hemoglobin was 9.5 Gm, and red blood cells numbered 2,500,000. The total blood proteins were slightly diminished and the albumin-globulin ratio was 0.88. Blastomyces were demonstrated in direct smear from a milium abscess of the right hand. In 2 of 4 mice inoculated intrascrotally with a suspension of biopsy material in isotonic solution of sodium chloride there developed lesions in the lungs and mesenteric lymph nodes, containing a great number of organisms. Cultures on Sabouraud's medium were overgrown by saprophytic bacteria.

The patient has received four whole blood transfusions. The ulcerations were cleansed with hydrogen peroxide, bathed with bichloride of mercury and dressed with 20 per cent sulfathiazole ointment. The left hand was straightened with general anesthesia and placed in a basswood splint. Infra-red radiant heat was used in treatment of the decubitus. In the interval from May 12 to September 25, the patient received a total of 1,279.0 Gm of iodide salts, most of it in the form of intravenous injections of 10 per cent sodium iodide, rapidly and conspicuously the patient improved. Iodide therapy was discontinued on September 25, because new asymptomatic firm verrucous nodules were devel

oping on his hands, forearms and face. Since the discontinuance of the iodide therapy these lesions have apparently regressed. Clinically, the differentiation of these lesions from iododerma tuberosum was rather difficult. However, a biopsy specimen taken on October 8 still showed budding spores in the granulation tissue. The inorganic iodine content of these lesions, determined by microchemical analysis, was not increased over that of the unaffected skin (iodine was 32 per cent in ash of the lesion and 53 per cent in ash of the unaffected skin).

The patient continues to have periods of constipation and incontinence of the feces, but has gained considerable weight and strength.

The presentation included microscopic sections of cutaneous lesions and of the lung of the inoculated mouse, roentgenograms of the lung and bones of the patient and of the lung of the mouse and several clinical photographs of the patient.

DISCUSSION

Dr LOUIS A. BRUNSTING, Rochester, Minn. In blastomycosis cutis, the organism may be recovered from the urine and from the prostatic secretions, as occurred in a case recently presented at the September 1946 meeting of the Minnesota Dermatological Society in Rochester. The patient had characteristic lesions on the skin of the face, and there were no symptoms of systemic blastomycosis. The organism grows readily on ordinary soil, which may be of epidermologic significance.

Dr STEPHEN ROTHMAN. This patient has had huge doses of iodides, the total exceeding 1 Kg of sodium iodide in four months. He had done very well as far as his general condition is concerned, and many of the lesions have healed during the massive iodide therapy. Still, in many places the process shows signs of activity. I plan now to combine the administration of iodides with vaccine therapy. In vitro experiments have shown that iodides have no fungicidal effect on blastomyces. The effect must be an indirect one, the iodides probably act primarily on the granulation tissue, as in tertiary syphilis.

Multiple Congenital Defects, Von Recklinghausen's Disease (?)

Presented by Dr F. E. SENEAR and STAFF

R. H., aged 9, was referred for dermatologic consultation from the Department of Pediatrics, University of Illinois Research and Educational Hospital. There was a history of retarded mental and physical growth, speech difficulty and impaired hearing. Examination revealed (a) small stature, (b) moderate brownish pigmentation of the skin, most pronounced on the face, neck and chest, and depigmented split-pea-sized vitiliginous area scattered throughout the pigmentation, (c) epicanthus, (d) absence of thumbs, (e) lumbar lordosis and bilateral congenital dislocation of the hips, and (f) dental hypoplasia. There was a cafe-au-lait spot in the periumbilical region.

Results of laboratory studies of cellular and chemical components of the blood were negative. Roentgenograms showed the absence of the first phalanx and metacarpals but revealed no other abnormality.

DISCUSSION

Dr THEODORE CORNBLEET. I thought of the possibility of Rothmund's syndrome to fit this little girl's condition. Thannhauser has recently referred to it as heredofamilial atrophic dermatosis (Thannhauser, S. J. *Ann Int Med* 23:559 [October] 1945).

A Case for Diagnosis (Granuloma Pyogenicum?) Presented by DR CLEVELAND J WHITE

Sporotrichosis Localized Lymphangitic Type Following a Hangnail Which Became Infected While the Patient Was Working in the Garden Presented by DR CLEVELAND J WHITE

Carcinoma (Erysipelatodes) Presented by DR F E SENEAR

About three and a half years ago, the patient had a tumor removed from the right thigh. Approximately three weeks later, roentgen treatments were instituted, and she received one treatment daily for twenty days, the duration of the treatments being twenty minutes on each occasion. After this course, the skin in the treated area became covered with crusts, healing did not take place, and gradually the present condition developed.

On most of the outer aspect of the right thigh, the patient presents a peculiar picture, the skin being replaced with a coarsely mammillated area, heavily crusted in places. At the periphery, there are many small rounded areas, the size of a b-b shot to a large pea, with crusting on top. Removal of the crust revealed some pus beneath. This mammillated area has several semisolid rounded elevated vegetated-appearing growths of about almond size.

The specimen of tissue removed three and a half years ago consists of an amputated section of skin, elliptic in shape, measuring 9 by 6 inches (23 by 15 cm). In the central portion of the skin, there was an elevated area 7 mm above the surface of the skin with a rather serpiginous outline and coarsely granular surface, it was dark brown to light green. The periphery of the section was firm, whereas the more central area was rather soft, and the cut surface was translucent in appearance. The structure was confined to the cutaneous surface, as multiple sections through the tissues did not reveal any gross penetration into the subcutaneous tissue. However, at one point near the margin, there was a small area suggestive of an extension beneath the dermis. Sections were taken from this area for more study, and the diagnosis was non-cornifying, squamous cell carcinoma of high grade malignancy.

DISCUSSION

DR H E MICHELSON, Minneapolis. I believe this to be a pagetoid type of cancer. I cannot understand why the glands are not involved, for one would expect that.

DR M R CARO. The invasion of the lymphatics was of the type that is seen in recurrent carcinoma of the breast following removal and irradiation, the type called carcinoma erysipelatodes.

Dermatomyositis Presented by DR F E SENEAR

DISCUSSION

DR PAUL A O'LEARY, Rochester, Minn. The term sclerodermatomyositis is applicable to this type of the disease, because evidences of cutaneous sclerosis and dermatomyositis are both present. This patient presents the terminal phase of the disease.

We have seen 2 patients with dermatomyositis in whom have developed the Cushing syndrome, hirsutism, acne, hypertrophy of the genitalia and cutaneous purplish striae, after the dermatomyositis had been present several years.

Surgical intervention was not thought advisable in either case, and it is now not possible to determine the relationship

DR F E SENEAR I had not seen this patient for some months until today, and I have never had her under care or observation. She came in originally with a striking picture of erythema on the extensor surface of each forearm, which was so pronounced that I thought some one had given her ultra-violet radiation or that she had been lying in the sun with gloves on. She came back in three weeks and again several weeks later, at which time she had the same lesions on the dorsal surface of the hands. Dr Oliver saw her, and we both felt that she had typical early lupus erythematosus. When we saw her the next time the picture of erythematous lesions had changed to one of a lichenoid type of lesion. At that time she had no complaint with regard to weakness. Later I noted in the history that about six weeks before we saw her she had muscular weakness and debility. It was so slight that she did not point it out to us. She did start out with symptoms that might have been symptoms of dermatomyositis. The muscle biopsy revealed signs of dermatomyositis. I had not seen her for a year, and the last time I saw her she did not show signs of poikiloderma.

Pseudoxanthoma Elasticum Presented by DR S ROTHMAN and (by invitation) DR E L LADEN

Hyperhidrosis Presented by DR D F WEBER and DR IRENE NEUHAUSER

H D, an office worker aged 33, has been troubled with sweating of the palms and soles since boyhood. His sweating continues during the night, although it is less in amount than during the day. His palms are continually moist. The sweat is cold to the touch.

Local treatment has been with aluminum chloride, 25 per cent solution, and roentgen rays. His sweating has not been lessened, and his disease has proved obstinate to all therapy. Additional therapeutic suggestions would be appreciated.

DISCUSSION

DR PAUL O'LEARY, Rochester, Minn. When dyshidrosis is severe enough to interfere with the patient's earning a living a sympathectomy should be considered.

DR M R CARO I have been told by psychiatrists of several cases of extreme hyperhidrosis that were amenable to treatment by psychoanalysis. I would suggest that, before any radical surgical procedure is carried out, the patient be referred to a psychiatrist for study.

Marcus R Caro, M D, President

Leonard F Weber, M D, Secretary

Nov 20, 1946

Madura Foot in an American Negro from Tennessee Presented by DR M H EBERT and (by invitation) DR J GRAFFIN

Systemic Actinomycosis Presented by DR FRANCIS E SENEAR and STAFF

L C, a white man aged 35, is a patient in the Department of Surgery, University of Illinois Research and Educational Hospital, admitted with a diagnosis of chronic empyema. There was a history of pulmonary symptoms and weight

loss since April 1945. Rib resection had been performed for drainage of an empyema, following which a perinephritic abscess and an inflammatory mass developed in the right lower quadrant of the abdomen and required operation. His condition has become progressively worse in spite of surgical treatment, sulfonamide drug therapy, large doses of penicillin and roentgen therapy. A diagnosis of actinomycosis was made on October 24. There are fistulas draining clear glairy serous fluid at the site of the operative scars in the chest and abdomen. Sulfur granules are visible in the expressed pus.

DISCUSSION

DR IRENE NEUHAUSER. I understand that there are about thirty-two different types of aerobic *Actinomyces bovis* which occasionally cause Madura foot.

DR STEPHEN ROTHMAN. As I understand from the British literature, all cases of Madura foot are caused by *Actinomyces*. Madura foot in India is so common because the people all go barefooted.

DR IRENE NEUHAUSER. Most of the malignant types are caused by asteroid, but in most of them there is secondary involvement. The bovis type of *Actinomyces* is the most malignant.

A Case for Diagnosis (Pityriasis Rubra Pilaris?) Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR J GRAFFIN

DISCUSSION

DR J F MADDEN, St Paul. I did not believe that this was pityriasis rubra pilaris. There were 2 cases when I was at the University Hospital at Ann Arbor, Mich., and Dr Wile stressed the point that when pityriasis rubra pilaris occurred in the scalp it was particularly purulent and extended down in a mask over the neck. It did not show the discrete lesions that are present in this case. Other men have stressed the presence of lesions on the fingers which this boy did not have. It would be a good thing to discuss this case with the one of congenital ichthyosiform erythroderma shown from the University of Illinois, because it will bear out the point which I have made. The man from Illinois did not have scalp lesions. If he did, one might have thought it was pityriasis rubra pilaris. I think that the first case is probably one of psoriasis, but I did not see the slide.

Cutaneous Horn of the Scalp, 5 Cm in Length Presented by DR THEODORE CORNBLEET and (by invitation) DR D COHEN and DR J GRAFFIN

Localized Myxedema Presented by DR M H EBERT and (by invitation) DR N L BAKER

M C, 20 year old Negro woman, a factory worker, had exophthalmic goiter in 1944. In August 1945, a partial thyroidectomy was performed, but the symptoms of thyrotoxicosis did not abate. Six months ago, painless swellings, which itched occasionally, appeared on the legs.

The blood pressure was 160 systolic and 100 diastolic, and the pulse rate ranged from 80 to 120. Mild weakness of the extensor muscles of the thighs was found. There was moderate exophthalmos, and a thyroidectomy scar with slight keloid formation was present. The thyroid was enlarged, the right lobe measuring approximately 8 by 5 cm and the left 5 by 5 cm. On the anterior and lateral aspects of both legs in the lower half there were irregular, firm, moderately elevated plaques measuring up to 5 by 5 cm. The skin over these was pigmented and the follicles were dilated, giving the appearance of pigskin.

The hemogram and urine were normal. The Kahn reaction of the blood was negative. The total blood protein was 7.2 Gm and cholesterol 245 mg per hundred cubic centimeters, with 75 per cent cholesterol esters. The blood chlorides were normal and the nonprotein nitrogen 28 mg per hundred cubic centimeters. The basal metabolic rate was +45 per cent on admission and is now +24 per cent after nine days of treatment with thiouracil.

DISCUSSION

DR FREDERICK R SCHMIDT. Two years ago I presented a case of localized myxedema before the society. At that time I said that I did not think the term localized myxedema was a very apt one. As O'Leary and others showed several years ago, the term solid edema of the legs fits the disorder better. The word myxedema connotes a hypothyroid condition which is not the case, and treatment with thyroid or iodine does not improve the symptoms.

DR STEPHEN ROTHMAN. The word myxedema is very confusing, because this lesion is definitely not a manifestation of hyperthyroidism. We know today that this lesion occurs only in hypothyroid persons. It does not clear up with the clearing of the thyrotoxicosis. Exophthalmos is a sign which cannot be eradicated by thyroidectomy. I have seen patients with more exophthalmos after than before thyroidectomy. It is something which has to do with hyperthyroidism but is not a direct consequence of it, it probably has something to do with the pituitary gland.

DR FRANCIS E SENEAR. I think that if the name is changed it would be inadvisable to call it solid edema, a name which already belongs to another type of disease.

DR M H EBERT. In a recent issue of the *British Journal of Dermatology*, there is a report of a young soldier who had atypical thyrotoxicosis. In just two or three pages the author gives about as good a discussion of the disorder as I have ever read. He discusses, particularly, the terminology. The name he adopts is myxedema circumscripta thyrotoxa. It is a circumscribed myxedematous condition which occurs invariably in cases of thyrotoxicosis.

It is well known that the pituitary may be associated with myxedematous degeneration. He states that thiouracil seems to act on the pituitary, 1 or 2 patients with severe disease were treated without effect, and consequently one cannot blame the pituitary entirely. In England, Dunhill reported a number of cases, in 1 of which there was some operative work done on the pituitary without any effect on the myxedema thyrotoxa. I think that more work must be done before we understand the potentialities of the disease.

Sarcoidosis Presented by DR HERBERT RATTNER and (by invitation) DR H RODIN and DR N L BAKER

Boeck's Sarcoid Presented by DR DAVID V OMENS and (by invitation) DR H D OMENS and DR N L BAKER

Lupus Miliaris Disseminatus Faciei Presented by DR OLIVER S ORMSBY

The patient, Mr D G, was shown before this society at its December 1945 meeting. A description of the lesions with the history can be seen in the transactions published in THE ARCHIVES.

DISCUSSION

DR H E MICHELSON, Minneapolis The opportunity is offered to compare the 2 Negro patients and try to decide whether they have the same disease. The first patient said that she was entirely well and able to carry on her duties in the usual fashion. The tuberculin reaction was positive with 1:100 dilution. I think that one could accept that particular case as one of sarcoidosis. The second patient was ill, fatigued very easily and was unable to carry on her work except with effort. There were a number of papules on the skin, and the vermilion border of the lip was involved. Many changes were seen in the lungs. The tuberculin reaction was negative. The glands were very much enlarged.

Does this disease in Negroes belong in the sarcoid group, and how can one prove it? Workers in New York seem to think that every patient such as the second one may have tuberculosis. In this case I suggest the Charpey treatment, which can be given with impunity.

The case presented by Dr Ormsby is a good one with which to compare the last case.

Exfoliative Dermatitis (Lipomelanotic Reticulosis?) Presented by DR HERBERT RATTNER and (by invitation) DR H RODIN and DR J GRAFFIN

Mr P T, aged 67, a Syrian, who had always before enjoyed good health without any disease of the skin, had an infected foot in March 1946. After several days of treatment at home, he entered the Cook County Hospital with cellulitis of the right foot, dermatitis of both legs, bilateral lymphangitis and lymphadenitis, with several sinuses on both thighs from which drained purulent material. In three weeks, when the infection had subsided, the patient left the hospital, although he still had acute dermatitis of the legs. He returned in ten days with generalized exfoliative dermatitis with intense pruritus.

The color of the skin has since changed from bright red to deep dark brown. The patient has lost 35 pounds (16 Kg) in weight and continues to have severe pruritus and chilliness, which usually can be relieved by adequate doses of diphenhydramine hydrochloride.

There is now generalized exfoliative dermatitis, the skin is dark reddish brown, and there is generalized lymphadenopathy, but the liver and spleen are not palpable. The blood pressure is 94 systolic and 50 diastolic, the temperature is normal, and the cardiac examination shows no abnormality. The urine is normal, and the Kahn reaction of the blood is negative. The blood is normal except for 8 per cent eosinophils.

Sternal puncture revealed a shift to the left in granulopoiesis, with an increase in eosinophils but no changes of diagnostic importance. Roentgenograms of the chest and sella turcica showed no abnormalities. The electrocardiogram showed evidence of anterior myocardial infarction. The fasting glucose level was 60 mg per hundred cubic centimeters with a normal sugar tolerance curve. The basal metabolic rate was +22 per cent. Chemical examination of the blood showed total protein 6.2 Gm per hundred cubic centimeters, with a normal albumin-globulin ratio, blood serum 135 mg per liter (138 to 148), potassium 26.4 mg (17 to 22) per hundred cubic centimeters and nonprotein nitrogen 37 mg per hundred cubic centimeters.

Histologic sections of the skin and lymph node are presented.

DISCUSSION

DR S W BECKER This man obviously has had and still has exfoliative dermatitis. The sections show a pronounced superficial perivascular infiltrate and

a number of cells containing melanin. These are the cells which give the grayish cast to the skin. The melanin is absorbed and carried to the lymph nodes. Whether the name given to the condition is justified is open to question. The patient's outcome will depend on the nature of the exfoliative dermatitis. If he has leukemia or any of the lymphoblastomas the outcome is not favorable. The cutaneous picture is the same as it would be if it were exfoliative dermatitis.

DR EDWARD A. OLIVER: I presented a case with that diagnosis about a year ago, and some of the members scoffed at the name lipomelanotic reticulosis. When Poitreau described it, he said that it was a peculiar pathologic condition existing in generalized eczema and generalized dermatitis, and occasionally (in 4 or 5 of his cases) with mycosis fungoides. Mycosis fungoides developed in the boy we saw in three months, and he died. I think that the diagnosis at autopsy was Hodgkin's disease, but I am not sure.

DR S. M. BLUEFARB: The histologic picture of the lymph node would fit in with what Poitreau described as lipomelanotic reticulosis. What is the eventual development in these cases? Although Poitreau saw the disease in only 11 cases, he stated that it was a benign cutaneous disease. In a later report he stated that mycosis fungoides had developed in his cases. Mycosis fungoides developed in Dr. Oliver's case, so that apparently the disease is not entirely benign. I think that this should be considered a new cutaneous disease divorced from pityriasis rubra pilaris. Haber classified it as a precursor to mycosis fungoides. Since in some of these cases mycosis fungoides does develop, which is a form of lymphosarcoma, I think that there is a definite relationship between Simons' disease and lipomelanotic disease of Poitreau.

DR HERBERT RATTNER: We presented this case because we knew that there was some discussion among pathologists as to whether the disease was an entity. It is interesting that Robb-Smith changed his opinion recently and has stated the belief that it is an entity.

Acute Disseminated Lupus Erythematosus Presented by DR HERBERT RATTNER and (by invitation) DR H. RODIN and DR N. L. BAKER

E. N., a 39 year old white woman, had influenza in December 1945, which was treated with one of the sulfonamide drugs. Within a few days there developed the picture of acute disseminated lupus erythematosus, with involvement of the face, scalp, neck, trunk and extremities, and a temperature of 103 F.

DISCUSSION

DR FRANCIS W. LANCH, St. Paul: I would like to comment on the administration of sulfonamide drugs. This patient had an illness for which she was given a sulfonamide drug, and in a few days the dermatologic picture of lupus erythematosus developed. We are all familiar with the work of the British authors reported a few years ago when the sulfonamide drugs came into use and were tried in lupus erythematosus. It was pointed out that sensitivity to sulfonamide drugs is present in such cases.

I should like to add another case of a patient with acute rheumatic fever to whom penicillin was given without effect. The medicament was changed to one of the sulfonamide drugs, and immediately thereafter the patient's condition changed and there was a sudden outbreak of acute nondisseminated lupus erythematosus. Death occurred a few days later, even though the administration of the sulfonamide drug was stopped. One should give more thought to the relationship between the

administration of the sulfonamide drugs and this disorder Most of us have given up the use of these drugs in this disease

DR ADOLPH ROSTENBERG JR (by invitation) In the main I think that Dr Lynch's remarks should be phrased differently I do not believe that there is any relationship between administration of sulfonamide drugs and lupus I think it more accurate that in any toxic process there is more likely to be a sensitivity in toxic persons The sensitivity does not result only to sulfonamide drugs, such persons will react to any agent

DR FRANCIS W LYNCH I do not agree I meant to convey the idea that the relationship is more specific than Dr Rostenberg pointed out

DR A H SLEPIAN (by invitation) I had occasion to observe a great deal of sensitization to sulfonamide drugs during the war In a group of inductees who were given sulfonamide drugs, my co-workers and I found that in 25 per cent there developed a rash which we were able to prove was due to the sulfonamide drugs I think that this is in accord with Dr Rostenberg's remarks

DR STEPHEN ROTHMAN I would like to support the idea that sulfonamide drugs have a specific action Penicillin did not seem to produce sensitization in the cases in which I saw it given

Generalized Herpes Zoster Associated with Lymphatic Leukemia Presented by DR T CORNBLEET and (by invitation) DR D COHEN and DR N L BAKER

Circumscribed Scleroderma (en Coupe de Sabre). Presented by DR M H EBERT

Morphea and Cutis Hyperelastica Presented by DR STEPHEN ROTHMAN and (by invitation) DR A L SHAPIRO and DR E LADEN

Morphea Presented by DR STEPHEN ROTHMAN and (by invitation) DR HELEN KRYSA

D S, a 29 year old white housewife, in September 1945 reported with a hard lump in the right breast of one year's duration

On physical examination, a cutaneous-subcutaneous mass, 4 by 5 cm, was felt in the right breast A biopsy of this mass was made and the histologic examination revealed chronic inflammation

The present lesion originated at the site from which the biopsy specimen was taken and has spread from there around the nipple in both directions There is a lesion of the right breast surrounding the nipple in a half-moon shape, it consists of an indurated plaque with yellow discoloration and atrophic surface In most places it is surrounded by a lilac ring A section of the skin shows fibrosis and homogenization of collagen in the papillary and subpapillary layers Routine laboratory tests did not reveal any pathologic changes

DISCUSSION

DR OLIVER S ORMSBY Morphea is a disease that terminates in a certain amount of atrophy It should not be treated with roentgen rays or radium When atrophy occurs, it is often attributed to the administration of roentgen rays or radium I have seen 2 or 3 patients with morphea on the breast which was diagnosed as carcinoma by the surgeon and operation performed Morphea is not uncommon, does not amount to much or cause any particular harm, and it does not matter what treatment is used except roentgen rays and radium The saber blade type of

morphea is not uncommon. One end becomes broader and goes up, often to the back of the scalp, and the skin in that location is very white. It has the same course as ordinary localized scleroderma.

DR STEPHEN ROTHMAN The interesting point in the history of the woman with morphea is that it started after the mass was removed, which was not scleroderma but a subcutaneous mass. In comparing the disease in the 2 cases with the bandlike scleroderma, I feel that these are different entities, that the bandlike scleroderma starts early in life and is more or less progressive, whereas typical morphea is a connective tissue formation, mostly starting in adult life, with the number of lesions increasing and becoming larger.

A Case for Diagnosis (Cribriform Lesions of the Hands) Presented by
DR M H EBERT

Panarteritis Presented by **DR EDWARD A OLIVER** and **ASSOCIATES** from Hines Hospital

D R, a white man aged 19, stated that in April 1945 he noted painful swellings of the legs, chest and arms. Successive crops of red lesions would occur, the old lesions remaining present. The nodules kept increasing in number and were tender and swollen. They were more painful when he was ambulatory, he believes that cold weather aggravated the symptoms.

Physical examination reveals areas of a mottled, purplish blue eruption on the anterior aspects of the left side of the chest, extensor aspects of both arms, flexural aspects of both thighs, especially the right, all aspects of both legs and on the dorsum and sides of both feet. Numerous subcutaneous nodules of various sizes are palpable in these areas, some of which are painful to pressure. The skin of both legs, especially the right, is tense and somewhat indurated.

The histologic examination of a section removed revealed an inflammatory process which involved all the arterioles and some of the veins. In some instances the process is characterized by panarteritis, in which all layers are involved. The cells of the infiltrate are lymphocytes, monocytes and occasional polymorphonuclear leukocytes and eosinophils. One of the larger arterioles is thickened almost to the point of obstruction, with evidence of thrombosis. Practically all the vessel walls show some degree of thickening and varying degrees of infiltration. In some vessels the infiltrate is definitely perivascular and involves the surrounding fat and connective tissue. There are suggestive hyaline changes in the walls in some instances.

Periarteritis Nodosa Presented by **DR OLIVER S ORMSBY**

Mrs A C C, aged 22, had her disorder for eleven months. There has been a mild degree of anemia since the onset of menstruation. Rheumatic fever occurred at the eighth or ninth year and lasted for several months. The present trouble started in February 1946. The examination of the blood made by **Dr Pernokis** last July showed no significant changes. The general examination of the chest, colon and stomach revealed no pathologic changes. The heart was normal. The first cutaneous manifestation consisted of edema on the left leg from ankle to knee. This was painless at first, but was accompanied with continuous pain later, sharp and shooting in character. Small raised patches developed which were sensitive to touch. These gradually became more sharply circumscribed, but would subside in about a week, leaving a purplish red area, which is still present. At the same time an aching pain, with muscular weakness of shoulders, arms, forearms

and hands, appeared. On the left side of the chest there was one small erythematous patch. In addition, painful nodules have been present on the trunk, back, left shoulder and buttocks. No lesions remain on the back. There is a very faint pale reddish purple livedo patch on the left side of the chest. There are faint purplish, smooth, noninfiltrated patches on each buttock and on the lateral dorsal surface of each forearm near the wrist, another small patch on the right leg and several on the left leg, with raised small painful nodular lesions on the right leg. There is a biopsy scar on the left leg.

Tissues sent by Dr H R Prentice to Dr C V Weller, Professor of Pathology, University of Michigan, showed slight muscle fiber degeneration and moderate interstitial fibrosis. Small vessels are thick-walled, and some appear occluded with proliferative endothelial reaction. The stroma is increased between the muscle bundles. The lesions are primarily vascular and are seen in various stages from necrosis of the walls to complete obliteration by organization. These changes are compatible with periarteritis nodosa.

DISCUSSION

DR M H EBERT. I presume that panarteritis means periarteritis. This was so extensive that it might be called panarteritis. The only point I want to call attention to was present in both cases. It was quite evident in the young man, but less so in the young woman. These were the lesions on the left side of the chest. There was an area that would correspond to livedo reticularis due to interruption of the circulation. In this case it was due to narrowing or complete closure of the arteries that supply the area. A similar picture occurs with injection of a bismuth preparation into an artery, but there it is more advanced and results in necrosis.

DR HAROLD SHELL (by invitation). I saw 2 cases of periarteritis nodosum in an army general hospital during a pathologic conference. These cases had terminated fatally. The pathologic changes were characteristic in the liver, spleen and kidneys. There was nothing unusual in the skin. Overseas I saw a case similar to the one presented by Dr Oliver, in which the man had a rather small erythema-nodosum-like eruption which lasted four or five days, underwent involution and then recurred. Biopsies were performed, and the pathologic department returned a diagnosis compatible with periarteritis nodosum. This man was not ill in any sense, and physical examination disclosed nothing except prodromal urticaria. In the other 2 cases that had terminated fatally there were no prodromal symptoms except rather evanescent urticaria, in one case lasting two days and in the other, three days.

DR EDWARD A OLIVER. Our pathologist at Hines Hospital is responsible for the name panarteritis, I do not know what it means. Not having seen many cases of periarteritis nodosum, I am inclined to think that this is such a case. As Dr Ebert pointed out, the first thing we noticed was the livedo reticularis type of skin, more pronounced a few weeks ago than today. One could palpate the individual vessels and could feel the nodose-like lesions, which were very tender and painful, over all these vessels.

DR OLIVER S ORMSBY. It is a rare disease as far as dermatologic experience is concerned, though not so rare otherwise. It is also very serious, at least 90 per cent of the patients succumbing to it. When it attacks the internal organs death occurs. In the patient shown today the lesions were typical of the nodular type. The nodules occur over the blood vessels on the legs, arms and in parts of the body. They are very much alike, are very painful and they show no signs of

undergoing involution. This patient received penicillin without effect and then arsenic without beneficial effect. She was given arsenic together with some vitamins, and in two or three months the eruption had practically cleared up. About two or three weeks ago numbness developed in the arm with wrist drop. Her physician decided that it was arsenical in origin and stopped the arsenic therapy. In a few weeks the eruption recurred. In spite of the fact that she had an arsenic reaction, I think that arsenic will again be given.

DR ADOLPH ROSTENBERG JR (by invitation) You are all familiar with the work of Rich at Johns Hopkins Hospital on the experimental production of periarthritis nodosa. It is predicated on a sensitization mechanism. If this is the case, and in view of the fact that many of these cases eventuate fatally, it might be well to try the new antihistamine drugs. I think that tripeleminamine hydrochloride (pyribenzamine®) or diphenhydramine hydrochloride (benadryl®) should be given a trial in any case in which a diagnosis of periarthritis nodosum is made.

DR FRANCIS W LYNCH, St Paul I had a case in which that treatment failed.

DR OLIVER S ORMSBY This patient had that treatment with no beneficial effect. I have been using arsenic in this disease, and I have seen cases that cleared up with that treatment when everything else had failed. One can give the Asiatic pill (arsenous acid and black pepper) over a long period in large dosage without interruption of treatment. We use the pill made by Parke Davis and Company, which contains 1/9 grain (7 mg) of trioxide of arsenic.

Generalized Telangiectases Following the Use of Pyribenzamine® Presented by DR. MAURICE OPPENHEIM (by invitation)

A T, a white man aged 53, has a generalized eruption which began on the legs. In July 1946 he was treated for a generalized itching cutaneous eruption which was diagnosed as urticaria erythematosa chronica and which he had had for several months. He was given calcium internally and calcium injections once weekly. He applied a lotion containing coal tar solution. With this treatment he did not get any relief from the itching. He was then given tripeleminamine hydrochloride (pyribenzamine®) by mouth, 50 mg four times daily for seven days. This aggravated the eruption, and the patient was referred to me.

At this time his entire body was covered with morbillous erythema, partially coalescent, mostly on the flexor areas, scalp and face. He had an intense itching on the entire body. He received calcium gluconate injections every other day and locally boric acid, alcohol and talcum. On September 30, two days after I saw him, desquamation began to occur all over the body. The itching began to subside. On October 7, there appeared all over the body telangiectasia, which I first thought were petechia. On pressure and raising of the arms, they disappeared completely. On mild friction or on points of pressure the redness was increased, and the scaling disappeared completely. On rubbing the skin vigorously, the superficial layers of the skin were removed. Leukoplakia was present on the inner aspects of both cheeks. The blood and urine were normal. The Kahn reaction of the blood was negative.

Histologic examination of a biopsy showed the epidermis to be normal and the papillary layer somewhat flattened. There were many new-formed capillaries, some enlarged, there was very little round cell infiltration.

DISCUSSION

DR FREDERICK R SCHMIDT When I first began to use the antihistamine drugs my fears were twofold, first, that they would act on the vascular system and

some time produce an irreversible action on the blood vessels and that there would be a permanent dilatation of the blood vessels. This was brought home to me by the case of a young woman to whom I gave pyribenzamine.² She immediately experienced a scarlatiniform erythema, with extreme itching, and was rather ill but recovered. My second fear has not been so well grounded, I thought that compounds containing the benzene ring might depress the leukocyte formation. That was borne out in a patient at Alexian Brothers Hospital to whom a considerable amount of benedryl³ had been given. The man did not feel well, and a routine blood cell count disclosed that the leukocytes were down to 3,000, and the differential stain showed that there was not only leukopenia but relative neutropenia.

DR. FRANCIS W. LYNCH, St. Paul. Several possible diagnoses come to mind in this case, but none of them are satisfactory. I wonder whether the case might be related in some manner to those described by Parkes Weber as telangiectasia mucularis eruptiva perstans. In this case there is more than the telangiectasia, there is an infiltrate, and that was true in Parkes Weber's cases. The presence of urticarial features in this eruption might also be related to the Parkes Weber cases. In that group there was a possible relationship to urticaria pigmentosa. The distribution of the eruption in his cases was not entirely like that, but most of the eruption was on the upper part of the trunk, and that holds true here. We should admit that, but bearing in mind that we are discussing morphologically the eruption.

DR. FREDERICK R. SCHMIDT. I do not believe that the presence of the infiltrate mitigates in any way against a diagnosis of irreversible vascular reaction.

DR. MAUPICE OPPENHEIM (by invitation). I have to correct the diagnosis a little bit. This is an annular eruption, like a port-wine nevus with many newly formed capillaries. I agree with Dr. Lynch that there are many inflammatory symptoms. It was striking to me that there was very little round cell infiltration. This is the first time that I have seen such a case.

The patient cannot raise his hand or arm to his head. If the skin is rubbed, hyperemia results. If the skin is squeezed one can remove the epidermis as in pemphigus chronicus.

A Case for Diagnosis (Pigmented Purpuric Lichenoid Dermatitis?) Presented by DR. FRANCIS E. SENEAP and STAFF.

Scleredema Adultorum Presented by DR. H. H. RODIN (by invitation)

Mrs. C. N., a white woman aged 52, was first seen on Oct. 25, 1946, complaining of swelling and stiffness of the skin of the face, chest and abdomen. She stated that it began six weeks before as a swelling of the neck which obliterated the cleavage lines and spread upward to the face and downward to involve the entire chest wall, including the upper portion of the abdomen and finally involving the arms and forearms. About three weeks prior to the onset of her present condition, a sore throat and headache developed which were treated with sulfonamide drugs. This illness lasted only about forty-eight hours.

Her childhood and medical history was essentially normal. Her surgical history revealed a cholecystectomy and appendectomy in 1937, a hemorrhoidectomy in 1940 and a cystocele repair in 1945.

The examination revealed nonpigmented, noninflammatory, nonpitting solid edema involving the face, neck, trunk, arms and forearms. The cleavage lines of the neck and face are obliterated, producing a masklike appearance. There is

some limitation of movement of the shoulder joints, as evidenced by moderate difficulty in the abduction of the upper extremities

Examination of the peripheral blood on November 16, revealed 5,540,000 red cells, 8,400 leukocytes and 88 per cent hemoglobin, with a differential count of 60 per cent polymorphonuclear cells, 2 per cent nonsegmented forms, 58 per cent segmented forms, 30 per cent lymphocytes, 2 per cent eosinophils and 8 per cent monocytes. The red cells appeared normal. The average cell diameter was 7.4 microns. The urine was normal except for several white blood cells. The result of the Mazzini flocculation test on the blood on November 11 was negative for syphilis.

DISCUSSION

DR STEPHEN ROTHMAN: I think that it is a classic case of scleredema. I saw 1 case in Berlin, and at that time attention was called to the fact that the most pronounced changes were seen in the shoulder. The patient today presented the most notable changes around the shoulder. It is evidently due to some collagenous changes in the tissues. It comes on after an infectious disease, and most of the cases are reported as occurring after a severe influenza.

DR CARL W. LAYMON, Minneapolis: I agree with everything Dr. Rothman said, but I have a little word of warning. Some of these cases of scleredema last from fifteen months to two years. There have been cases reported in which there have been as many as three or four recurrences.

Nevus Acneformis Unilateralis Presented by DR J. H. MITCHELL and DR R. H. SCULL

Nevus Comedonicus Unilateralis Presented by DR S. ROTHMAN and (by invitation) DR S. A. WALKER

Melanoma (Eight and One-Half Months Postoperatively) Presented by DR E. A. OLIVER and DR S. M. BLUEFARB

M. J., a white woman aged 59, was shown at the February 1946 meeting of the Chicago Dermatological Society with a diagnosis of melanoma. She had a verrucous lesion of three months' duration, superimposed on a pigmented mole of many years' duration. She was operated on the latter part of February 1946 and the microscopic sections of the lesion revealed a highly malignant melanoma. To date she has shown no signs of recurrence. Microscopic sections and koda-chrome® slides are shown.

DISCUSSION

DR JOHN F. MADDEN, St. Paul: In my opinion one cannot make a diagnosis of malignant melanoma microscopically. There are many melanomas that are not malignant that are diagnosed as malignant melanomas, and that is especially true in the young. The younger the person the more inaccurate the diagnosis based on microscopic observation. My co-workers and I have in our group any number of cases in which a diagnosis of malignant melanoma was made in a child and a poor prognosis given to the parents, and the child lived on and on.

DR S. W. BECKER: I had the pleasure of attending a conference in New York city last week at which the pathologic aspects of atypical and normal pigment cells was discussed. Dr. Pack made a point that I never knew before, that malignant melanoma never occurs before puberty. There is a period in the patient's life just beyond puberty when melanoma will grow.

In the case shown today was a lymph node removed with the tumor? That is important. If one removes the tumor and then strips the skin between the tumor and the lymph node and then removes the lymph node, the patient has less chance of having a recurrence.

DR F E SENEAR I would like to ask Dr Becker whether, on the basis of Dr Pack's statement, one could presuppose that there would never be any danger of stimulating the dissemination of the nevus if one removed it before puberty.

DR S W BECKER Dr Pack emphasized, as most surgeons do, that moles be excised widely. He recommends that they be removed before puberty, and then the child will not have a melanoma. The question is far from settled, and there are many points that are not understood.

DR M R CARO I have had occasion to go through the sections of pigmented moles and nevi with our general pathologist. He feels that there is always danger of recurrence in the malignant form. The pathologists all feel that pigmented moles are potentially malignant and should be excised widely.

DR E E SENEAR A few years ago Brues pointed out that in the malignant type of nevus he was able to show extension of cells far beyond the pigmentary element, and if only the pigmentary element is taken out some of the cellular elements are missed.

DR EDWARD A OLIVER I can tell about a mole by looking at it carefully. If it is a black or blue mole and there is any question about it, the lesion should be widely excised. Others can be safely treated with the ordinary cautery.

A Case for Diagnosis (Alopecia Prematura? Cutis Verticis Gyrata?) Presented by DR S W BECKER

Mrs C R, aged 34 years, has noted thinning of the hair, more pronounced on the vertex, for ten years. She does not know about her father's hair, but her uncles have had no tendency to baldness. She formerly menstruated once yearly, but later, after treatment, she menstruated every seven weeks. She has a clearcut history of tetany, evidently of the idiopathic variety, and the blood calcium (7 mg per hundred cubic centimeters) and blood phosphorus (8 mg per hundred cubic centimeters) corroborate this diagnosis. The basal metabolism test showed no abnormality. There was some slight suggestion of hair distribution of the male type. Because of redundancy of the scalp on the vertex, which suggested latent cutis verticis gyrata, a roentgenogram of the sella turcica was made, which showed no abnormalities. She presented fairly normal scalp hair on the periphery, but distinctly shortened hair over the vertex. The shortest hairs were about $\frac{1}{2}$ to 1 inch (1.3 to 2.5 cm) long, and in no place had they been replaced by downy hairs, as in the usual premature variety of male baldness. Microscopic examination of hairs showed slight hyperkeratosis about the hair root, which was small, but no evidence of fungous infection. The scalp over the vertex was thickened and more freely movable than on the periphery. The patient is now receiving systemic treatment with vitamin D and calcium.

DISCUSSION

DR STEPHEN ROTHMAN This type of alopecia is unusual because the maximum baldness is on the vertex. The patient has had difficulty with menstruation from early youth, menstruating only once a year or so. After eleven years of married life she became pregnant and delivered a baby. I think that there is some serious imbalance in this woman's sex organs. She has a general hypertrichosis, she has a definite moustache. The question is: Is there a pathologic change in the

adrenal cortex or should one assume that the adrenal cortex secretes more male sex hormone than is normal?

Juvenile Xanthoma Presented by DR OLIVER S ORMSBY and DR MICHAEL H EBFRT

Multiple Epithelial Cysts Presented by DR S ROTHMAN and (by invitation) DR S A WALKER

Congenital Ichthyosiform Erythroderma Presented by DR F E SENEAR and STAFF

T C, a white man aged 25 years, has been a patient in the Department of Dermatology, University of Illinois Research and Educational Hospital, since March 1939. Cutaneous changes and absence of sweating, except on the palms and soles, have been present since birth. The skin of the entire body is decidedly erythematous, and there is thick heaped-up yellow scaling, particularly over the joints and on both flexor and extensor surfaces. The midline of the body and the face are relatively free of scale, and the face has a greasy varnished appearance. There is bilateral ectropion, more noticeable on the right. Laboratory studies revealed nothing significant. The basal metabolic rate was +5 per cent.

A roentgenogram of the skull showed a normal sella turcica, and results of routine studies of the blood and urine were normal.

There was no sweat response to pilocarpine, but with thyroid medication temporary partial clearing of the skin occurred, and the patient reported some perspiration in the axillas and soles. Thyroid therapy was discontinued because of loss of weight.

Histologic examination of a biopsy specimen from the right arm showed a thick parakeratotic scale that was firmly attached to the epidermis, but which was separated into several lamellas by bloody crusts. The granular layer was missing. The epidermis showed considerable intracellular edema, especially in its upper portion, and a few mitotic figures. The rete pegs were irregularly elongated, broadened and in places fused. The basal layer was intact. The parakeratotic scale extended downward as a plug into the follicles. In the corium the sebaceous glands were apparently increased, and there was a slight cellular infiltrate just beneath the epidermis.

DISCUSSION

DR CARL W LAYMON, Minneapolis: I do not believe that the name ichthyosiform erythroderma is a good name, because it emphasizes the erythema. It is a disease with vesiculated ichthyosis. Several men have studied this condition, notably Richey and Burns, who feel that it is a part of ichthyosis fetalis. The severe type of ichthyosis fetalis ends fatally a few days after birth, but there is supposedly a milder type which is called ichthyosis fetalis, which is probably the same disease but without generalized ichthyosis. I thought that this was a classic example.

DR STEPHEN ROTHMAN: I do not quite agree with Dr Laymon, I think that there is always ichthyosis and that erythema is always present. I agree that it is the same type of genetic anomaly as ichthyosis fetalis. It is extremely important to differentiate it from ichthyosis fetalis, which is an entirely different disease in all respects, this being a highly recessive mendelian dominant and the other an irregular dominant. There are histologic differences between the two. The erythroderma really comes out in those cases and in the cases in which the condition is not fully developed. Sometimes it is difficult to make a diagnosis. I had a patient who was treated for some allergic condition over a period of three or

four years and was on a very restricted diet I found a family history of ichthyosiform erythroderma congenitum I mention that to point out that the inflammatory changes are symptomless

DR F E SENEAR The extreme amount of keratosis which this patient shows is a recent development When we saw him originally he had a very erythematous face, with a varnished bar look and with an ectropion During the past few years we have not seen him He reported a week or so ago showing this pronounced keratotic element

Marcus R Caro, M D, *President*

Leonard F Weber, M D, *Secretary*

Dec 18, 1946

Mycosis Fungoides Presented by DR M H EBERT and (by invitation)
DR J GRAFFIN

A Questionable Case of Lupus Vulgaris Treated with the Charpy Method
Presented by DR M H EBERT and (by invitation) DR N L BAKER

A S, an 11 year old Negro boy, was presented before this society in October 1946, the diagnosis of lupus vulgaris was accepted, although biopsy specimens were not typical of tuberculosis Granulomatous tumors have been present on the nose and in the nose for the past nine months, for the past six months similar lesions have been present on the upper lip On the soft and hard palates there had been four translucent bodies, 5 mm in diameter He was treated with penicillin intramuscularly and sulfadiazine and various wet packs and ointments, but the condition steadily progressed Since Oct 19, 1946, he has been receiving ertron® (irradiated ergosterol) 50,000 unit capsules twice daily Improvement was first noted November 7, nineteen days after this treatment was begun The granulomatous enlargement of the nose has disappeared, there is slight destruction of the tip of the nose and the alae, with atrophy of the epidermis and slight crusting at the sites from which the biopsy specimens were taken

DISCUSSION

DR STEPHEN ROTHMAN I did not believe that a diagnosis of lupus vulgaris could be made My co-workers and I treated 2 women with the Charpy method, and both are getting along remarkably well We are doing studies of calcium content and chemical content of the blood There is a tremendous absorption of the infiltrate due to this treatment

DR C W FINNERUD It was my impression that at the October meeting we were well agreed clinically that the disease was lupus vulgaris If I am not mistaken, the section is the same as shown at that time It shows nothing except a proliferation of the epithelial cells in a small area From the results of the treatment I must say that this boy is very fortunate His skin looks entirely different now than it did a couple of months ago It is also probable that other conditions may respond to the Charpy treatment I still think that this is lupus vulgaris, in spite of the fact that it cannot be verified histologically

DR M H EBERT Clinically this is a typical case of lupus vulgaris We must evaluate the Charpy treatment on the basis of the clinical results, and they have been marvelous in this case

Sarcoidosis? (Tuberculosis?) of the Skin in a Negro Woman Presented
by DR T CORNBLEET and (by invitation) DR H SHORR and DR N L BAKER

DISCUSSION

DR ARNL KLEM, Oslo, Norway' The term sarcoidosis is new to me I always called it Boeck's sarcoid Boeck was the first one to give a description of this sickness, and I think that his name should be kept The diagnosis is not easy A countryman of mine has discovered a new test, the so-called Kveim test It is like the Ducrey test and easy to make A papule results, like the sickness itself, which comes after weeks, sometimes two or three months, and sometimes later I hope that you will work with this test and try to find out whether you are of the same opinion as Dr Kveim

DR M H EBERT That brings up the question of the relationship of what is called sarcoidosis and tuberculosis I do not believe that there is any question that the lesions on the face are clinically sarcoid The type of sarcoid seen in the Negro consists of small papules, almost all on the nose but sometimes on the eyelids and on the back of the neck In the classic case the tuberculin reaction is negative and the histologic picture is that of sarcoid This is the case here If it was originally sarcoid something has happened to the patient's response to tuberculin, because the tuberculin reaction is positive instead of negative Active tuberculosis is present in the bones of the leg, and the tubercle bacilli were recovered from the sinus tract Looking at the section, the major portion looked like a lymphocytic infiltrate I do not know from what area the biopsy specimen was taken In the section there was a small crust One would expect to see that in true sarcoid It may be that since the reaction of the patient has changed, the histologic picture of the lesion has changed in the meantime

It is still a question whether sarcoid is of tuberculous origin Sarcoid structure is not specific for any one disease Structure of that type occurs in tuberculosis and in syphilis I personally think that this is sarcoid I am of the opinion that the sarcoid seen in the Negro is tuberculous in origin In this instance the response changed and the reactions changed, so that the patient now has a positive tuberculin reaction and her old tuberculosis has been activated

DR THEODORE CORNBLEET The patient has had tuberculosis of the bones for some time The changes shown here could be accepted by those favoring tuberculosis as the cause of sarcoid and by those on the other side Here is a woman with a frank tuberculosis of the bone, and yet she has what clinically looks like an ordinary case of sarcoidosis of the face This woman has a high degree of sensitivity to tuberculin, something which we have seen before in sarcoidosis, especially in Negroes Perhaps we will take more biopsy specimens from the facial lesions to see whether there are any further changes from a sarcoid picture to that of frank tuberculosis

Malignant Melanoma with Generalized Metastasis and Changes of the Central Nervous System Presented by DR T CORNBLEET and (by invitation) DR D COHEN and DR J GRAFFIN

Papulonecrotic Tuberculid Presented by DR M EBERT

Ulerythema Pyogenicum Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS

A Case for Diagnosis (Possible Bizarre Residuals of Secondarily Infected Seborrheic Dermatitis, Lupus Erythematosus?) Presented by DR F E SENEAR and STAFF

Parapsoriasis en Plaques (Brocq) Presented by DR DAVID V. OMENS and
(by invitation) DR HAROLD D OMENS

B L, a 15 year old boy, presents a generalized eruption on the body, less pronounced on the extremities, of variable-sized dark red scaling patches, with mild infiltration of the involved skin, some of which have coalesced to involve large areas. This condition is of five years' duration or more, with no subjective sensations. The family history is noncontributory. The boy is an only child, and there is no history of cutaneous disturbance in the parents.

The Kahn reaction of the blood was negative. No fungi were found on examination of the scrapings. Histologic examination revealed a disorganization of the stratum corneum with parakeratosis. The stratum granulosum for the most part was indistinct or absent, there was pronounced acanthosis with intercellular and intracellular edema and liquefaction degeneration of the basal layer, the corium was edematous throughout with dilatation of the lymph and blood vessels with a cellular infiltrate which was perivascular, composed of lymphocytes and some leukocytes and extending into the papillae.

DISCUSSION

DR F E SENEAR I thought that this was an interesting picture but not too easily classified. I thought of the possibility of parakeratosis variegata or parapsoriasis lichenoides rather than the en plaque type. The lesions were made up of narrow, diffuse erythematous, very slightly raised patches, with none of the papular element of the lichenoid type. I do not recall seeing parapsoriasis of the en plaque type with so much confluence as on the abdominal wall and on the flanks. With this extensive involvement, it seems to me that the infiltrate was more than is usually seen in parapsoriasis of the en plaque type. The history of absence of symptoms and response of the eruption to therapeutic measures would fit in well with the diagnosis of the en plaque type of parapsoriasis. I cannot think of any alternative diagnosis. Dr Caro said that the histologic picture was not a good one for parapsoriasis, and yet, as I recall the writings on the histologic changes of that particular disorder, it was evident that the diagnosis could not be made with microscopic study alone. I think that clinically the disease belongs in that group. I did not regard the eruption on the right hand, consisting of one definitely annular lesion and eight or ten smaller papules, as being part of the picture. Some of these papules were distinctly brownish. I felt that this was early lichen planus. I think, also, that the lack of involvement of the extremities in this case is a point against the en plaque type of parapsoriasis, because ordinarily one sees considerable involvement of the lower extremities. Here, it stopped sharply at the lower part of the thighs.

DR M R CARO The histologic features of parapsoriasis en plaque are not characteristic, and the diagnosis cannot always be made on the basis of the slide alone.

DR CLARK W FINNERUD I did not see the section. Although clinically I could not diagnose the disease as parapsoriasis, I could not make a definite diagnosis either. I thought that possibly the lesion of the hand, in spite of the short duration, might be related to the body eruption, in that I have seen, particularly in Negroes, patches of diffuse scaling dermatitis with much infiltration in which fungi have been found. I think that the skin should be carefully studied for fungi. My impression also was that the blood should be carefully studied. This may be a slow oncoming manifestation of one of the lympho-blastomas.

Lichen Sclerosus et Atrophicus Presented by DR F E SENEAR and STAFF

DISCUSSION

DR OLIVER S ORMSBY Clinically this is almost a classic case. I have been interested in these cases for many years because I had the privilege of publicizing this disease in this country. Previous to 1912 this type of disorder had never been described in America. It had been described abroad, but not under this title. There were a group of three or four types of conditions that had been reported under the title of "white spot disease." That was the title that was used for all these lesions with white spots, including this disease. At the time I worked on it I reported 6 cases under the title "Lichen Planus Sclerosus et Atrophicus." In the last few years my co-workers and I have omitted "planus," because we felt that it was not a form of lichen planus. At the time we wrote the original paper we concluded that the disease in all these cases was of one or two types, but occasionally there was a third type. It was either lichen sclerosus or morphea. It is difficult sometimes to distinguish between these two disorders. They both occur more often around the shoulders, on the back of the shoulders and in the low lumbar areas than anywhere else. Occasionally the eruption is more extensive. It is often symmetric, but not always. In general, the disease is rather restricted in its manifestations. A few groups of lesions occur, and after a certain number of years they clear up and leave white atrophic areas. In 1 of the first classic cases I had, there were white papules, and in each papule there were two to five black keratotic plugs. While all the lesions were individual and well defined, several of them were in patches. In the patches one could pick out the individual white lesions. When a patch of morphea guttata and a patch of lichen sclerosus et atrophicus occur, one sometimes has difficulty in distinguishing between the two. I saw a patient with these enlarging white spots. After about fifteen years she came in with typical morphea on the leg. That puzzled me, because I had always claimed that there was no connection between morphea guttata and this disease. I still think so, and I think that the morphea developed independently on the leg and that it had nothing to do with the woman's original trouble. Once in a while the lesions become rather extensive.

There is only one other disease to be considered, and that is the disease reported by Sahli which is characterized by generalized white papules which are flat and which have degrees of whiteness. In lichen sclerosus the white papules are whiter than anything that occurs on the skin. They look as though whitewash had been spilled on the skin. I saw one of those cases in Dallas, Texas, a few years ago. The histologic changes were different than those of lichen sclerosus, and the condition was different. That may have been an anomalous case of lichen sclerosus. The lesions are rather superficial and never develop into anything else.

DR F E SENEAR I saw this patient for the first time this afternoon. Not infrequently in these cases of lichen sclerosus et atrophicus lesions are found in the genital region. I saw such a patient recently with involvement over the scapula, and, on examination, I found an extensive involvement of the vulva and an area about the size of a coffee cup surrounding the anal area. If one had seen the anogenital lesion alone, one would have had no hesitancy in making a diagnosis of kraurosis vulvae.

A Case for Diagnosis (Moniliasis Aphthae of the Mouth?) Presented by
DR F E SENEAR and STAFF

Subacute Disseminated Lupus Erythematosus Treated with Streptomycin.

Presented by DR CLEVELAND J WHITE and (by invitation) DR ROBERT C RANQUIST, DR HENRY S CAMBRIDGE and DR C A NOVY

R N, a Mexican girl aged 13, was first seen on Nov 6, 1946, complaining of an eruption on the face and forearms and pains in various parts of the body. Examination revealed a diffuse erythematous margined butterfly eruption on both sides of the nose, numerous erythematous macules on each cheek and some on various areas of both extremities. She complained of malaise, pain in the joints and lack of appetite. Her temperature when she was first seen was 103.6 F. A clinical diagnosis of subacute lupus erythematosus of the disseminated type was made, and hospitalization was advised.

In the hospital, with rest alone, her temperature dropped gradually to 101 F, and at the end of two days the pains in the joints had subsided somewhat. At this time 1,000,000 units of streptomycin were given daily for ten days. By the fifth day the temperature had dropped to 99 F and thereafter became normal and remained so. A soothing lotion was used on the various areas, and the eruption started to disappear soon after the administration of the streptomycin. She was dismissed from the hospital November 27. When last seen, on December 10, there was a brownish black discoloration at the site of the original butterfly region of the nose. A roentgenogram of the chest was normal. The reaction to the Mantoux test was negative. A section was taken from a lesion on the right elbow on November 18 and a slide prepared. The parents would not give permission for a biopsy at an earlier date.

When the patient was first admitted to the hospital, her leukocyte count was 3,900. It gradually increased, so that on the third day it was 6,000, and when she was dismissed from the hospital it was 10,700. The other constituents of the blood were normal. The Kahn and Wassermann reactions of the blood were negative. The urine showed some albumin on admission, but was entirely clear at the time she left the hospital.

The case is not presented to claim cure due to streptomycin, but to show what happened in 1 case in which it was administered. It is hoped that its use may abate the more serious developments in such cases.

DISCUSSION

DR F E SENEAR: I do not wish to be too critical of any type of treatment that might be available for lupus erythematosus. Dr Rothman has had good results with huge doses of penicillin. My co-workers and I have had good results in several cases with penicillin, usually combined with plasma or small amounts of blood in transfusion. Dr O'Leary has discussed their therapeutic results, and Dr Louis Brunsting, in a symposium on therapy, discussed the subject; his conclusion was that rest in bed was the only thing that was of any avail in this disease.

Calcinosis Circumscripta with Lupus Erythematosus Disseminata.

Presented by DR F E SENEAR and STAFF

DISCUSSION

DR STEPHEN ROTHMAN: It is remarkable that in these cases one never finds any abnormality of the blood calcium level. The phosphates and phosphatase are normal.

DR THEODORE CORNBLEET In this patient the protein was changed and there was an elevation of the albumin-globulin ratio. The feeling is that the protein should always be studied when a calcium determination is done. There was a change in the sedimentation rate. One can visualize the possibility of calcium spilling out in certain places, especially around the ankles and in places where the circulation is slow and where it is known that calcium will precipitate out.

DR STEPHEN ROTHMAN I do not agree with what Dr Cornbleet said. I understand that this patient has lupus erythematosus, so that it is understandable that there is an elevation of the albumin-globulin ratio and a high sedimentation rate, but I do not think this explains the calcium deposits. One practically never sees calcium deposits due to albumin-globulin shifts or to a high sedimentation rate. I do not see how this would explain the deposits of calcium in the tissues.

DR THEODORE CORNBLEET I am not explaining the precipitation of calcium only on that basis. It is well known that protein has something to do with calcium metabolism and that there is a change here. Undoubtedly there are other changes. One does not find that there is calcinosis in a patient with elevation of the albumin-globulin ratio or in patients with lupus erythematosus. It is just one peg on which the whole thing can be hung.

DR M. BRUNNER (by invitation) In reviewing the literature I found that there has been no previous description of calcinosis circumscripta occurring in association with lupus erythematosus disseminata.

Favus in a 5 Year Old Child Recently Arrived from Europe Presented by
DR SAMUEL J. ZAKON and (by invitation) DR AARON L. GOLDBERG

Marcus R. Caro, M.D., President

Leonard F. Weber, M.D., Secretary

Jan 15, 1947

Extensive Calcinosis of the Chest Wall and Shoulder Presented by Dr
MICHAEL H. EBERT and (by invitation) DR J. GRAFFIN

Disseminated Lupus Erythematosus with Ascites and Normal Urine in a Negro Woman Aged 47 Years Presented by DR. D. V. OMENS and
(by invitation) DR HAROLD OMENS and DR J. GRAFFIN

Lupus Erythematosus of the Disseminated Discoid Type (Unusually Extensive and Destructive) Presented by DR F. E. SENEAR and STAFF

A Case for Diagnosis (Lupus Erythematosus of the Eyelid) Presented by DR P. P. BOSWELL (by invitation)

Chronic Discoid Lupus Erythematosus?* Presented by DR PAUL A. O'LEARY, DR HAMILTON MONTGOMERY and DR LOUIS A. BRUNSTING and
(by invitation) DR ROBERT R. KIERLAND, Rochester, Minn.

Generalized Lichen Planus with Atrophy Presented by DR THEODORE CORNBLEET and (by invitation) DR D. COHEN and DR J. GRAFFIN

*Presented at the meeting of the Minnesota Dermatological Society, Rochester, Minn., Sept 15, 1946

A Case for Diagnosis (Lichen Planus? Lichen Nitidus?) Presented by
DR S W BECKER

A Case for Diagnosis. Presented by DR THEODORE CORNBLEET and (by invitation) DR H SCHORR and DR N L BAKER

R K, a white man aged 25, had measles and severe pertussis as a child. At the age of 12, ulcers appeared on the tonsils. From that time on, ulcers appeared on the tip of the tongue, the lips and the pharynx. The lesions begin as pinhead-sized white spots, enlarge until they are finger nail size and then ulcerate. The entire course is three to six weeks. He thinks that they occur at the onset of a cold or during a period when he is "run down." In December 1937 the only attack of extraoral lesions occurred. Ulcers appeared on the glans penis and the inner aspect of the legs, at the same time lesions were present on the vermilion border of the lower lip. In January 1946 a course of 300,000 units of penicillin cleared up an attack of ulcers of the mouth.

The orifice of the mouth is diminished in size by scarring, particularly at the angles. There is hypertrophic scarring of the tip of the tongue and the gingival aspect of the lips. There is mild pyorrhea alveolaris. On the glans penis there are similar scars, and on the inner aspect of the lower third of both legs there are dime-sized scars.

The Kahn reaction of the blood was negative. The urine and blood were normal, as was a roentgenogram of the chest. The sedimentation rate was 16 mm per hour.

Periadenitis Mucosa Necrotica Recurrens Presented by DR F. E. SENEAR and STAFF

D S, a white woman aged 52, has been troubled with recurring, painful ulcers of the mouth for the past ten and one-half years. The ulcers are preceded by small painless nodules beneath the mucosa. On healing of the ulcers, scars are formed, in fact, this cicatricial process has been so severe that a narrowing of the external opening of the mouth has been produced.

Smears from the ulcers have shown a few fusiform bacilli, gram-positive cocci and gram-positive bacilli but no spirochetes.

The blood and urine and a roentgenogram of the chest were normal. The Kahn reaction of the blood was negative.

The patient has been treated with crude liver extract, vitamins and repeated smallpox vaccinations, but the attacks of ulcerations have recurred. Recently she was given paraaminobenzoic acid, 2 Gm daily, which was later increased to 5 Gm daily. At first we felt that this medication was controlling her attacks, but on Jan 14, 1947, she returned with a new crop of ulcers.

DISCUSSION

DR LOUIS A. BRUNSTING, Rochester, Minn. Ulcerated lesions of the mouth associated with ulcerated lesions of the genitalia occur more commonly in women than in men. They have been called aphthous lesions. Some time ago we were interested in the etiology of these lesions, and Dr E. T. Cedar studied them with the idea of identifying them with a virus disease such as herpes simplex. A number of other etiologic factors have been considered. Skin tests and elimination procedures showed that 1 patient with lesions in the mouth and on the scrotum and a history of sensitivity after eczema was sensitive to chicken. I should

like to ask Dr Rostenberg what can be accomplished in these cases by a study of the reactive mechanism, call it allergy or what not

DR ADOLPH ROSTENBERG JR I cannot contribute much to the question Dr Brunsting asked I would suggest that he study the bacteriologic picture and try to find a method of making extracts, getting them from the organisms when he possibly can

DR MINNIE PERLSTEIN We have seen a group of patients with allergic ulcerations in the mouth One patient reported on by Dr Wien and myself had an ulcerated lesion in the mouth and one on the vulva which were definitely on a psychosomatic basis She was cured by treatment along this line and has remained well for twelve years Three other patients had routine skin testing, one was definitely sensitive to oatmeal and the eruption cleared when this was omitted from her diet The other patient was sensitive to coffee and would have a recurrence whenever she took coffee In the third patient the reactions to all the skin tests were negative I saw the patient from the Cook County Hospital when she was first admitted The entire buccal mucosa was ulcerated She improved on receiving heavy doses of vitamin B I have not seen her for two months and did not see her today We had a man at the clinic who improved when treated with vitamin B

DR JAMES R WEBSTER We must assume that these lesions of the mouth have a multiple origin One patient, a physician, had repeated attacks of adenitis I was unable to do anything for him He was in charge of a laboratory, and he cultured a hemolytic staphylococcus from the lesion He was treated with the sulfonamide compounds, and the periadenitis lesions immediately cleared up He has had no recurrence in four years There are scars from the previous lesions

DR MAURICE OPPENHEIM (by invitation) Dr Lipschutz, who studied the bacteriologic picture in these cases, did not observe lesions in the mouth

DR FRANCIS W LYNCH, St Paul, Minn I should like to make two comments which may not be of immediate significance One is the clinical similarity of a single lesion to periarteritis nodosa That fits in with the remarks on allergy Again, one of these lesions has a vascular reactive process which results in a superficial necrosis which heals slowly, with scar formation The second comment has to do with a patient whom our group will remember, a woman who had lesions for many years and was relieved after a febrile illness Subsequently she had a relapse, and we gave her fever therapy, which gave her relief, at least more than one would expect from an ordinary fever itself I do not recommend that as a form of treatment for the lesions

DR THEODORE CORNBLEET My understanding is that some of the patients reported on under the title of Lipschutz disease did have lesions in the mouth I do not know whether the original author reported them, but subsequent authors have been trying to spread out this entire group and have attached such names as Behcet's syndrome and Sutter's syndrome and recently Reiter's name has been attached to some of them In this syndrome there are ulcerations together with changes in the joints I like to think that in some of these cases there is a kind of Arthus phenomenon I think the bacteria may be attributed to constitutional changes which are out of proportion to the local findings even though they may be somewhat severe

DR F E SENEAR We are in thorough accord as to the complex etiologic factors in these cases For some time we have made a practice of sending all these patients to the department of allergy In some cases we are able to determine

some direct causative agent in the way of foods In others we have seen, as Dr Perlstein reported, frank improvement after the use of vitamins

With regard to the question of lesions in the mouth in association with *Bacillus crassus* lesions of the vulva, we all recognize that that type of patient may have lesions of the mouth associated with disease of the vulva

A Case for Diagnosis (Halogen Eruption, Granulomatous Lesions of the Legs) Presented by DR THEODORE CORNBLEET and (by invitation) DR D COHEN and DR N L BAKER

A Case for Diagnosis Presented by DR M H EBERT and (by invitation) DR N L BAKER

J S, a white man aged 69, was admitted to the Cook County Hospital because of hypertension He had had a bad cold a month ago and was given red tablets and a brown liquid medicine by his physician Three weeks ago he noticed painless nodules on the face, arms and legs

His blood pressure was 196 systolic and 96 diastolic There was sclerosis of the peripheral arteries and of the retinal arteries On the face and on the extremities there were many superficial and subcutaneous nodules, match head to filbert size In the main they were firm and nontender A few on the legs were tender and fluctuant On the posterior aspect of both arms there was a chain of subcutaneous, firm, fixed nodules up to hazelnut size The posterior cervical lymph-nodes were slightly enlarged

Thick yellow-green pus was aspirated from two of the fluctuant lesions on the legs, no fungi were found in a sodium hydroxide preparation of this material The urine was normal The Kahn reaction of the blood was negative There were 4,850,000 erythrocytes, a hemoglobin content of 71 per cent and 9,200 leukocytes, with 66 per cent polymorphonuclear leukocytes, 1 per cent basophils, 22 per cent lymphocytes, 11 per cent monocytes with poikilocytosis and occasional target cells The nonprotein nitrogen was 36 mg per hundred cubic centimeters The roentgenogram of the chest revealed a heart with hypertensive contour and no enlargement The Mantoux test (dilution, 1 to 10,000) gave a positive reaction

(His physician informed us that the medicines he was taking were aminophylline and digitalis)

DISCUSSION

DR JOHN F MADDEN, St Paul, Minn The case is most unusual The nodules are pustular in some instances In spite of the history that some medicine had been taken, there is the possibility of a generalized bromide reaction The other possibility is that of reticuloendotheliosis, and the third is a halogen infection, with some local focus I would not offer any diagnosis although I thought of those three possibilities I would lean much more toward the diagnosis of a manifestation due to some internal medication

DR S W BECKER The patient exhibits an interesting problem I was impressed by the fact that these lesions appeared cryptic I wonder if that could constitute an abnormal reaction to the bite of a bedbug Certainly the inflammatory reaction and the round cell infiltrate are not enough to suggest leukemia In tick bites there is sometimes a severe round cell infiltrate I would suggest that the history be gone into carefully

DR ROBERT L BARTON, Dubuque, Iowa (by invitation) I was much impressed by the chain of nodules that this man had along the surface of both arms They are generalized nodules arranged along a linear distribution subcutaneously I

do not know about the man's general condition, but one thing that came to mind was periarthritis nodosa

DR FRANCIS E SENEAR I had a wild thought, thinking of the type of sporotrichosis in France in contrast to the type we see here I have never seen an instance of the generalized type described in the French literature, and that occurred to me as something that might be thought of as a possibility

NOTE—This was later proved to be a case of sporotrichosis by cultures The response to therapy was rapid and complete

A Case for Diagnosis (Infectious Dermatitis of the Chest?) Presented by DR M H EBERT and DR J R WEBSTER and (by invitation) DR N L BAKER

A Case for Diagnosis (Tuberculous Granulomatous Lesions on the Right Leg?) Presented by DR EDWARD A OLIVER and (by invitation) DR M D HARTMAN

A Case for Diagnosis (Lupus Erythematosus?) Presented by DR CLEVELAND J WHITE

Dermatitis Herpetiformis Presented by DR STEPHEN ROTHMAN and (by invitation) DR Z FELSHER

C J, a 61 year old white man, was first seen at the University of Chicago Clinics on Dec 31, 1946, because of an intensely pruritic erythematous and vesicular eruption, especially of the extremities, shoulders, chest and buttocks, of nine months' duration

Examination revealed scattered erythematous, edematous plaques and grouped vesicles on an erythematous base at the sites of involvement

The laboratory findings were as follows The urine was normal The Wassermann and Kahn reactions were negative The examination of the blood showed 4,640,000 erythrocytes, a hemoglobin content of 15.7 Gm and 5,100 leukocytes, with 67 per cent polymorphonuclear cells, 24 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophils

Patch tests with 30 per cent potassium iodide in petrolatum and with 50 per cent potassium thiocyanate (equimolecular) in petrolatum showed large bullae in twenty-four hours

The fact that the reaction to the patch test with potassium thiocyanate is as strongly positive as that to the test with potassium iodide indicates that the positive iodide reaction in dermatitis herpetiformis is due to decreased epidermal-dermal adherence resulting from peptization of the collagen This peptization is increased by iodide ions and even more so by thiocyanate ions

The response to sulfapyridine was immediate The patient was asked to stop taking sulfapyridine two days ago The present patch tests were applied yesterday

(NOTE—See Felsher, Z Studies on the Adherence of the Epidermis to the Corium, *Proc Soc Exper Biol & Med* 62 213-215, 1946)

DISCUSSION

DR JOHN F MADDEN, St Paul, Minn I agree with the diagnosis I think that the iodide test in dermatitis herpetiformis should be eliminated, because it is of no value whatsoever A number of years ago I studied our patients at the University and in my office There were 17 or 18 of these patients I gave them iodides by mouth and sodium iodide intravenously and ointments of varying strengths No two persons reacted alike, and no one patient responded the same way over a period of time, to the use of iodides In the majority the iodides had

no effect whatever in any period of the cycle Occasionally a patient would respond to iodides at a certain period of the cycle and three or four weeks later would show no response

DR UDO J WILE, Ann Arbor, Mich I saw nothing in this patient to justify a diagnosis of dermatitis herpetiformis There was no tendency toward grouping

DR STEPHEN ROTHMAN This case was typical of dermatitis herpetiformis The patient had a course of sulfapyridine and responded I do not know how accurate the iodine test is In our experience the reaction to the patch test for iodine is positive in 50 per cent of the cases The demonstration was done in order to show the nature of a reaction that might have occurred with dermatitis herpetiformis

Fox-Fordyce Disease of Recent Origin in a Man Presented by DR A W STILLIANS

DISCUSSION

DR STEPHEN ROTHMAN When we were looking at the patient one of the young men asked if the presence of apocrine glands meant Fox-Fordyce disease It does not necessarily mean this We had a case of ectodermal dysplasia in which all the apocrine glands functioned well If we give the sweating test to this patient it could be demonstrated where the apocrine glands are There is some atavistic change in this case which goes down from the breast to the navel It would be worth while to do a biopsy to see whether these nodules are associated with the apocrine glands

A Case for Diagnosis (Possible Cutaneous Metastases of Visceral Neoplasm?) Presented by DR F E SENEAR and STAFF

Eosinophilic Leukemia Re-presented by DR EDWARD A OLIVER and (by invitation) DR H RAY FULMER

The case, involving H B, a white man aged 26, was presented before this society as a case of eosinophilic granuloma at the October 1946 meeting After having received roentgen therapy as outlined here, the patient is again presented for your interest

High voltage therapy was begun on Oct 30, 1946, essentially as outlined by Dr W C Popp Treatment was directed posteriorly and anteriorly at both upper quadrants of the abdomen and to both sides of the pelvis The technical factors for each area of treatment were 140 kilovolts, 50 cm distance, 20 milliamperes and 0.5 mm of copper filtration, approximately 600 r being used The amount of treatment per day was 150 r to one field Each field was treated in order at approximately daily intervals until the total amount of treatment was given to each area This treatment was completed on Jan 14, 1947 In addition, he has received a course of superficial irradiation to the face, neck and both lower extremities The upper extremities were purposely omitted for purposes of control The technical factors used in the superficial therapy were 100 kilovolts, 30 cm distance and 5 milliamperes, no filtration being used The lower extremities have been given one treatment of 250 r The face and neck have been given six treatments of 88 r each

Fifteen leukocyte counts done during the thirty days preceding therapy averaged 21,600, with 31 per cent eosinophils The highest single count in that group was 36,000 leukocytes and 56 per cent eosinophils Daily white blood cell counts during the past two weeks show an average of 7,566, with 21 per cent eosinophils, the highest count being 9,700 and the highest eosinophil content

being 36 per cent. A sternal puncture done on Jan 9, 1947 showed normal fluid except for a rather large number of eosinophils. There was no infiltration of abnormal cells.

Photographs which were taken on Aug 24, 1946 are presented

DISCUSSION

DR UDO J WILE, Ann Arbor, Mich. When the patient was shown in October, the question was whether he had eosinophilic leukemia. I think the diagnosis of eosinophilic granuloma can be disregarded. At the time some of us thought it was a severe pustular eruption. If the patient had true leukemia, I would be surprised to see the amount of improvement that is present. I wonder whether the eosinophilia is as marked today as when we first saw him. I wonder if there are not other manifestations of leukemia. If not, I think a diagnosis of leukemia could not be made.

DR ASHTON L WELCH, Cincinnati (by invitation). I have had the privilege of seeing 3 patients—this one, 1 with Dr O'Leary and 1 at home. The last had dermatitis-herpetiformis-like lesions, and he had lesions consistent with a chronic infectious dermatitis. He had a white blood cell count that ran from 48,000 to 50,000, with an eosinophil content of 71 per cent at one time and of 50, 60 and 70 per cent for months. He did not respond to any treatment until we gave large doses of roentgen rays to the spleen. After that his blood count began to drop, until now his leukocyte count is 7,000. He had lost all his hair over the face and the whole body, but he has gained most of it back and part of his beard. The only other signs of leukemia were some nodules which at biopsy suggested lymphoblastoma but could not be classified specifically. He still has some enlarged glands in the inguinal region and small lesions interspersed with other lesions on the trunk. I think this is a little different from the specific type of lymphoblastoma with which we are familiar. The response to adequate amounts of roentgen rays is striking.

DR STEPHAN EPSTEIN, Marshfield, Wis. Like Dr Wile, I wonder whether a diagnosis of dermatitis herpetiformis can be ruled out. I cannot see anything which would rule it out. The patient has severe paresthesia of the elbows and feet, which accompanies dermatitis herpetiformis, his eosinophil content is high—it could reach 70 per cent in dermatitis herpetiformis and the white blood cell count could be high. The Löffler syndrome would fit in with dermatitis herpetiformis. In some cases sensitivity plays a role.

As to the roentgen therapy, the patient is not healed completely. He had no treatment to the arms or legs. The arms have improved. In leukemia the local treatment to the skin lesions is extremely effective. In some cases there is improvement from generalized roentgen treatment. I think the diagnosis should be left open until we have more proof one way or the other.

DR EDWARD A OLIVER. The patient was presented today to show the results of roentgen therapy as outlined by Dr Walter Popp of the Mayo Clinic. After Dr O'Leary saw the patient at the October meeting, he had Dr Popp write me concerning the method of treatment. The patient had no treatment of the long bones but he had treatment of the sides of the abdomen and the sides of the pelvis. We were to give approximately 600 r in divided doses. The improvement has been striking, and the patient is much better though far from well.

When he first came in we thought it was a severe case of dermatitis herpetiformis. He was given Fowler's solution (solution of potassium arsenite U S P) for a while, with no improvement, then sulfapyridine. Later on the picture

changed, and it took on the appearance of pemphigus. We administered stovarsol® (acetarsone), with no improvement. Then he began to show small mushroom-like tumors such as you see in mycosis fungoides. It was at that time that we showed him at the October meeting. On October 30 high voltage roentgen therapy was begun.

The diagnosis is still open. It is an interesting case. What is going to happen we do not know.

DR LOUIS A. BRUNSTING, Rochester, Minn. The significant finding in this case is the eosinophilia, but the diagnosis of leukemia is rather questionable because at no time were immature cells demonstrated. This is a remarkable form of reactive disturbance. Whether it could be classified as leukoplasic I cannot say. There are no changes in the bones.

Idiopathic Macular Atrophy Presented by DR STEPHEN ROTHMAN and (by invitation) DR H. KRYSA

Lichen Scrofulosorum Developing During Charpy Treatment for Lupus Vulgaris Presented by DR STEPHEN ROTHMAN and (by invitation) DR E. LADEN

Lupus Vulgaris Cured by Charpy's Method Presented by DR STEPHEN ROTHMAN and (by invitation) DR E. LADEN

M. S., a 35 year old white woman, became ill with tuberculous lymphadenitis of the cervical region in 1943. Her first lupus vulgaris lesion developed in a scar over one of the diseased lymph nodes. Later, new lesions developed over her face, back, arms and neck. She was treated in the outpatient department of the Albert Merritt Billings Hospital from August 1945 to July 1946 with a salt-free diet and local and general ultraviolet irradiation.

Improvement took place under this regimen. She then spent three months in New Mexico, and on her return most of the lesions had healed. Since specific infiltrates were still demonstrable in several lesions administration of calciferol, 150,000 international units daily, was started on Oct 28, 1946. By Dec 2, 1946, these infiltrates showed definite regression, and on Jan 6, 1947, they could no longer be seen. Serum calcium on January 8 was 9.4 mg and serum phosphorus 3.8 mg per hundred cubic centimeters.

A biopsy section of the skin showing tuberculous structure is presented. Inoculation of another piece of skin into guinea pigs revealed the presence of tuberculosis.

DISCUSSION

DR H. E. MICHELSON, Minneapolis. We agree that with the Charpy treatment some startling effects are obtained, with some spectacular ones and some that are not so good. I would rather discuss it in the abstract because it is a new treatment and we should not go to extremes. In reality, the treatment is not new because cod liver oil has been used for tuberculosis for many years. How does it work? Is the vitamin D a specific agent against the infiltration, or does it produce antibodies? The sections taken from some of our patients showed that there was not a vestige of infiltrate left behind.

In what types of tuberculosis should this be used? Since lupus vulgaris is a disease in which the patient has a high response, it might be dangerous to use it in patients who do not have a high response. We had bad results in adenitis. The factor of dosage, the interval, the length of time it should be used and the rest period should be carefully considered. Reactions may be local. The patients

may become worse, they may get a toxic form of reaction, or there may be metastasis. I think the future of this treatment will depend on the physicians who are using it. There should be a rigid diagnosis before it is used and microscopic sections before, after and during treatment. Thorough checks to see whether the patient has tuberculosis internally should be made.

DR F E SENEAR I should like to ask whether it is necessary to conform to the schedules so closely in the usage of the various types of medicaments. In this case there was a definite dose schedule, in regard to both frequency of administration and duration of treatment, and also a definite dosage, with the provision that the drug must be used in an alcoholic rather than an oil vehicle.

DR STEPHEN ROTHMAN As Dr Michelson said, side effects should be looked for. We should look for hypervitaminosis, which causes the patient to become suddenly sick, with a decline in phosphorus values. One should be exceedingly careful. The second side effect is a guide as to whether or not the patient has tuberculosis and whether this tuberculid was caused by tubercle bacilli. This patient had a tuberculid for years. At the same time she got extremely sick from the high dosage of the drug we gave her first. I think we have to follow the patient carefully. I was very much interested to hear that lymphadenitis was a dangerous side effect. We use exclusively the Winthrop preparation. The price of the oil solution is extremely high, and we soon started to use the capsule in which there is only one oil droplet. In the patient who had the lupus vulgaris the improvement came about during the administration of the capsules.

Blue Nevus of the Eye and Melanosis of the Temple (Due to Contact with Telephone Receiver?) Presented by DR STEPHEN ROTHMAN and (by invitation) DR G PINNÉ

A 20 year old Japanese-American girl entered the University of Chicago Clinics on Jan 6, 1947, complaining of a spreading bluish gray discoloration of the skin about the right orbit and cheek. This change commenced in April 1945.

At this time the patient was working as a telephone operator. She was accustomed to holding the apparatus to her right ear, using a mouthpiece suspended from the neck. A few months after she started this work, she noticed the appearance of blue spots on the temple. From there the disease slowly extended to its present limits. The patient remained an operator for nine months.

Throughout life she has had a black pigmentation of the sclera of the right eye. The pigmentation also existed on the conjunctiva of the lower lid. She has never taken headache powders or sedatives. Occasionally she takes *ex-lax*®. She has received no roentgen therapy. From time to time she uses Eau de Cologne, applying it to her hair and behind her ears. At night she uses a face preparation known as "Richter's cream."

She has had no serious illnesses but complains only of the ease with which she becomes fatigued.

There is a diffuse bluish gray pigmentation sprinkled with poorly circumscribed tiny spots of dark color on her right temple, right cheek, right side of the nose and periorbital region. The color does not change on glass pressure.

The pigment of the eye is situated in the sclera and the palpebral conjunctiva. The uveal tract is not involved. There are no abnormalities of the left eye.

The results of the laboratory examinations have yet to be reported. The chest was normal on fluoroscopic examination.

The examination of routinely stained sections showed melanin pigmentation in the basal layer only faintly. However, considerable hyperpigmentation of this layer can be seen in the sections treated with silver nitrate.

There were scattered perivascular and perifollicular infiltrates with round cells and histiocytes in the subpapillary layer in the mid-corium

Throughout the corium there were scattered chromatophores, partly in the form of macrophages. Comparing the silver section with dopa section, one can see that many pigmented cells in the corium were dopa positive and therefore must be regarded as melanoblasts

A Case for Diagnosis (Melanosis Following Roentgen Therapy of Pigmented Nevus?) Presented (by invitation) by DR S R MERCER and DR S W BECKER

Mrs A L, aged 33, had had a brown mole on the right side of her nose since the age of 2 weeks. Since the age of 1 year, the lesion has been frozen several times and then, at the age of 4, treated by some sort of "lamp," possibly roentgen ray. She presents a dark gray, atrophic telangiectatic plaque on the right of the ala nasi, with a small tumor in the lower portion and a brownish area at the superior portion, both of which have appeared in the last few months

DISCUSSION OF CASES OF DRS ROTHMAN AND PINNE AND DRS MERCER AND BECKER

DR HARRY R FOERSTER, Milwaukee. In the first case the question is raised of the possibility of contact melanosis and also melanotic pigmentation. I agree with the first diagnosis offered, that of a melanotic nevus of unusual type. I cannot conceive of a contact melanosis that would not be preceded by dermatosis, but there was no such history in this case. Also, the melanosis was not at the site of the most intimate contact with the telephone receiver. It was rather discrete, whereas pigmentation following contact dermatitis is much more diffuse. The pigmentation in this case was blue to slate blue rather than brown. It was identical in color with that in the eyeball which, I believe, is confirmatory of the nevoid origin. The fact that it is progressive I do not believe is necessarily a sign of any malignant tendency.

In the other case I believe that the pigmentation is nevoid rather than a result of roentgen therapy, even though there was some evidence of atrophy and a slight suggestion of telangiectasia. I have never seen roentgen pigmentation as intense as in this case or of this color. Roentgen pigmentation is more brownish. While there may be some roentgen change in the skin, such as atrophy, the pigmentation is the consequence of the progressiveness of the lesion rather than a result of therapy.

I believe this is still a benign lesion, but it should be kept under observation and no therapy attempted. I cannot conceive of anything that would be successful, assuming that therapy would be carried out after a diagnosis of developing malignant changes in a melanoma, other than an extremely wide surgical removal, such as was described by Dr Moe at Cleveland, and later plastic closure. I would consider it a benign lesion at present.

DR HAMILTON MONTGOMERY, Rochester, Minn. Dr Rothman's case was extremely interesting, especially in view of a case sent to me from a pathologist in Seattle. The patient was of Chinese extraction and had an extensive involvement of the entire side of the face and eyeball, with a histologic picture of chromatophores scattered in the nevus. They were not fused together as in blue nevus but separate as in Mongolian spots. We know that Mongolian spots occur in the Chinese and Japanese in 100 per cent of the cases. They are ill defined patches with ill defined margins that disappear in a few months to a year. There are cases in which the Mongolian spots have appeared elsewhere in the body and in which they have persisted into adult life. Dr Rothman's case is unusual

in that the lesion developed in adult life I do not think it is a blue nevus I think that this girl, who is of Japanese descent, is showing an unusual picture of Mongolian spots with typical dermatomelanotic cysts

DR MICHAEL H EBERT Some time ago Dr Slepian and I saw a case at Cook County Hospital The patient, a light brown woman, had a bluish discoloration of the ear I looked up the literature, and there was an article in a Japanese journal, evidently the condition is rather common in Japan because the author cited a large number of cases I do not recall what the histopathologic picture was in that case Dr Slepian today told me that while in the South Pacific he saw a number of these cases

DR STEPHEN ROTHMAN I am very grateful for the information Dr Montgomery gave that we can distinguish Mongolian spots by the fact that the cells are scattered in the corium whereas in blue nevus they have a more compact arrangement Dr Montgomery told me this was first differentiated in Jadassohn's Clinic in 1924

Dr Foerster's point is well taken, that the color of the skin lesion is the same as that of the sclera When one sees such a diffuse pigmentation I wonder whether one should not consider the possibility of a contact effect We do see such cutaneous accumulations of pigment early in contact melanosis

DR S W BECKER I think that the diagnosis in Dr Rothman's case is blue nevus and that Mongolian spots is the same thing, whether they are diffuse or patchy does not make any difference I wonder if the second patient might not have had a blue nevus to begin with She maintains it was a brown nevus and that she was only 1 year old when treatment was started She could have had an unusual combination of brown nevus and blue nevus, which sometimes occurs There is no history of roentgen therapy, though she says that at the age of 4 she remembers getting treatment from a lamp of some kind This to me suggests roentgen ray, and the telangiectasia suggests the same thing It is not inconceivable that under roentgen therapy the pigment might have been transferred from the epidermis to the dermis to produce this type of lesion

Alopecia of the Areata Type in Mother and Daughter Presented by DR JAMES R WEBSTER and (by invitation) DR FRANCIS HETREED

Dermatitis Repens of the Foot Presented by DR F E SENEAR and STAFF

Radiodermatitis of the Face Presented by DR EDWIN M SMITH JR

Sturge-Weber Syndrome Presented by DR EDWARD A OLIVER and DR SAMUEL M BLUEFARB

The Sturge-Weber syndrome consists of nevus flammeus, ipsilateral glaucoma (not present in this case) and cerebral symptoms (especially epilepsy), intracranial calcifications and contralateral hemiplegia The patient was a boy of 4 years

Favus of the Scalp in a Woman of 27 Born in Chicago Presented by DR L F WEBER and DR IRENE NEUHAUSER

Poikiloderma? Parapsoriasis? Presented by DR OLIVER S ORMSBY and DR MICHAEL H EBERT

Mrs J W, aged 35, has had the disease for eleven years She stated that the skin of her extremities always was more blue than normal Eleven years ago a red patch developed on the inner aspect of the left thigh Three years later a generalized eruption developed, which was diagnosed as contact dermatitis

from ivy This eruption is still present She has had soreness of the tongue for the same length of time She had a small tumor removed from the tongue one and a half years ago Also, she has had an eruption of the face She has had numerous skin tests but was not improved when the articles to which she was sensitive were removed

This patient has a bilaterally symmetric eruption which involves a considerable extent of the upper and lower extremities, the buttocks, the hips, the axillary folds and the neck In addition, there are a few scattered lesions on the rest of the trunk On the neck the lesions form a network of a brownish red color, the meshwork of which looks fairly normal On the upper extremities the eruption is more marked on the medial surfaces Here it seems to consist of closely set, shiny, flat-topped papules, dull red in color, many of which are covered with a fine scale These papules seem to be formed by an exaggeration of the normal lines of the skin in many cases The red color disappears on glass pressure, leaving a brownish background

On the rest of the upper extremities the papules are pinhead size, discrete and scattered On each elbow the papules are hypertrophic The anterior and inner surfaces of the thighs and the inner surfaces of the knees are markedly involved Here a definite infiltration is palpable Discrete, deep brownish red papules are arranged in a poorly defined network which in places coalesces to form a large irregular patch In the popliteal area and inner surfaces of the knees the superficial vessels in the papules are markedly dilated and angiomatous, but the red color disappears on glass pressure In places the angiomatous papules seem arranged in lines The satellite lesions on the trunk are pale brown maculopapules, covered by a fine scale which can be removed by grattage The patient has a livedo type of circulation on the extremities There are some telangiectatic vessels on the upper part of the cheeks over the zygoma The borders and tip of the tongue are redder than normal There is a dollar-sized hyperkeratotic patch on each sole and a pea-sized keratosis on the left palm

Histopathologic Nature of a Papule from the Posterior Axillary Fold—There is a laminated hyperkeratosis with discrete areas of parakeratosis In the epidermis the rete pegs have almost all been flattened out Areas where the rete mucosa is edematous and thickened alternate with areas where it is atrophic and thinned Generally speaking, the granular layer is normal except in places where it is absent or reduced to a single layer In one area there is so much intercellular edema that the border between the rete mucosa and the cellular infiltrate in the corium is difficult to make out This area is surmounted by a parakeratotic scale, and the stratum granulosum is absent There is a migration of leukocytes through the epidermis The subpapillary layer of the corium is edematous Many angiomatous blood vessels are present There is a moderate round cell infiltrate made up of lymphocytes and many histiocytes filled with pigment The iron stain for hemosiderin is negative The pigment is probably melanin

A section from a keratotic papule near the elbow shows similar changes with the exception that there is a dense parakeratotic plug which depresses the epidermis The angiomatous blood vessels are more numerous In the Weigert stained section the elastic tissue has largely disappeared from the papillary and subpapillary layers

DISCUSSION

DR F E SENEAR I thought that was one of the most striking pictures that we have seen today I felt that both of the diagnoses suggested would have to be given a good deal of consideration Dr Ormsby told me that the histopathologic diagnosis was poikiloderma, but on examining the patient clinically I did not

think the condition conformed to the usual clinical picture of poikiloderma. It seemed to me that clinically it might be placed in the classification of a type of parapsoriasis of which I have never seen a case, that is, parapsoriasis of the lichenoid type or lichen folliculitis of the variegata type. The description of that type of parapsoriasis and the clinical conception of different persons in different countries seem so indefinite that it is hard to form any idea about it. My feeling would be that this more nearly resembles my conception of parapsoriasis of the variegata type than the Jacobi type of poikiloderma vasculare. I felt that the atrophy was minimal as compared with the Jacobi type.

DR HAMILTON MONTGOMERY, Rochester, Minn. Dr Ormsby sent me the slides and his clinical description of the case. Histologically it resembles lupus erythematosus. It has been emphasized that poikiloderma resembles lupus erythematosus. Furthermore, dilated vessels appear after radiation, but this patient has had no radiation treatment. There is lichenification of the basal cell layer and there is degeneration in any type of parapsoriasis. The patient does not show the inflammatory reaction or lupus-erythematosus-like picture. I feel that histologically we can rule out parapsoriasis variegata.

DR STEPHAN EPSTEIN, Marshfield, Wis. I had occasion to see for the first time a case of parapsoriasis variegata characterized by three types of lesions, annular lesions, reticular lesions and lesions like those in erythema multiforme. I looked it up in the literature. Juliusberg feels that many of these cases that are first presented as poikiloderma eventually turn out to be parapsoriasis variegata. I took three specimens for biopsy in my case and sent them to Dr Pinkus. He said there was nothing resembling parapsoriasis variegata.

DR OLIVER S ORMSBY. I saw practically the first case of poikiloderma of Jacobi in this country. In that case there were lesions as large as my palm on the body and they looked like radiodermatitis. There were atrophic areas and hyperpigmentation. That was the characteristic lesion of that disorder. There has been a large number of cases of poikiloderma reported in the literature, and few of the patients have had poikiloderma. They have had symptoms like those of poikiloderma. A few years ago Dr Oliver presented a valuable paper on this subject reporting on cases of mycosis fungoides that in the beginning looked like poikiloderma and went on for some time with that diagnosis but eventually terminated in mycosis fungoides.

I have had considerable experience with parapsoriasis variegata, because I did work on cases with Coffey, who grouped three types of parapsoriasis under one name. I worked with that for a year. This patient presents some of the symptoms that are not found in a real case of parapsoriasis. During my experience I have seen a number of cases of poikiloderma of Civatte in which the lesions were on the sides of the neck. We do not consider those as being true cases of poikiloderma. I have seen cases with patchy telangiectasis, atrophy and not so much pigmentation. Those cases have been seen by the best physicians in the world, and nobody could be perfectly sure about the diagnosis. Histologically poikiloderma comes first in the case presented. Clinically some of the symptoms are those of poikiloderma and some are those of parapsoriasis. We will have to leave it as one of the unsolved cases.

Kaposi's Multiple Hemorrhagic Sarcoma (No Response to Many Types of Treatment Including Nitrogen Mustard) Presented by DR. F. E. SENEAR and STAFF

CLEVELAND DERMATOLOGICAL SOCIETY

L L Praver, M D, *President*

G W Binkley, M D, *Secretary-Treasurer*

March 28, 1946

Lepromatous Leprosy in a White Woman Emigrated from Syria Twelve Years Ago Presented by DR W R HUBLER and DR H K GIFFIN (by invitation)

Arsenical Keratoses in a Storage Battery Worker, No History of Ingestion of Arsenic Presented by DR R C LIGHT and DR J KAM

Extensive Neurofibromatosis Presented by DR R C LIGHT and DR J KAM

Subacute Disseminate Lupus Erythematosus with Renal Involvement. Presented by DR R C LIGHT and DR J KAM

A Case for Diagnosis (Mycosis Fungoides?) Presented by DR B HELD, DR M H GUSTAFSON and DR J BOWEN

A Case for Diagnosis (Granuloma Inguinale?) Presented by DR B HELD, DR M H GUSTAFSON and DR J BOWEN

Late Cutaneous Syphilis (Gumma). Presented by DR R C LIGHT and DR J KAM

Lichen Spinulosus Presented by DR E W NETHERTON

R W, a white boy aged 16, came to the Cleveland Clinic for observation for the first time when 5 years of age. At that time he had cheilitis exfoliativa. His mother had also had cheilitis exfoliativa for four years. This patient is presented now because of a follicular eruption on the trunk present for five years.

There are a number of rounded and irregular patches of a follicular eruption, on the chest, the lower portion of the sternum, upper part of the abdomen, upper part of the back and particularly on the lateral surfaces of the chest near the axillary folds. These lesions vary in size from 2 to 3 inches (5 to 7.5 cm) in diameter. They consist of grouped, discrete, follicular, large pinhead-sized pink to skin-colored acuminate papules, some of which contain hyperkeratotic plugs, while others contain a plug with the addition of a small threadlike spine, which extends well above the surface of the epidermis. Some of the plugs can be removed, leaving patent follicular orifices.

The biopsy showed that the epidermis was covered with a few layers of loose hyperkeratotic cells. The granular layer consisted of one layer of cells. There was one largely dilated follicle, containing loosely packed keratinized squamous epithelial cells. The dilatation was deep, extending downward for two thirds of

the length of the follicle. The sides of the dilated portion consisted of a thin layer of poorly staining epithelial cells. There was a perifollicular infiltration, consisting chiefly of lymphocytes. A serial section showed light to moderate perivascular infiltration of lymphocytes scattered throughout the upper portion of the corium. Sebaceous glands were absent in all sections. The treatment has consisted of vitamin A, 150,000 units daily since Jan 25, 1946, without change in the lesions.

DISCUSSION

DR H H JOHNSON There were some angular papules on the dorsa of the hands and on the flexor aspect of the forearm. There was also a small irregular white patch in the left buccal mucosa and at the left commissure of the mouth, such as is seen commonly in lichen planus. I propose the diagnosis of lichen planus for this patient.

DR G A DEOREO I agree with the remarks made by Dr Johnson. In 1895 Dr Pringle showed a series of patients with folliculitis and lichen planus. In 1939 a survey of the literature revealed a total of 21 cases. In 1940, Dr Wilbert Sachs and I reported 6 cases of lichen planopilaris (*ARCH DERMAT & SYPH* 45:1081 [June] 1942). We used the term lichen planopilaris of Dr Pringle, meaning lichen planus of hair follicles. The histologic changes are a dense infiltrate surrounding the hair follicles with the characteristic merging rendering the basal layer indistinct. In the histologic section presented today the changes about two papillae were consistent with lichen planus. I think that the condition presented is lichen planus involving the hair follicles.

DR F M McDONALD I agree with Dr Johnson, and I felt that the diagnosis of lichen planus should be principally based on an angular flat top papule on the dorsum of the hand and a white superficial papule. It is well known that lichen planus may be associated with other types of lesions. The patient does not give an accurate history, but I suggest further questioning for the possibility of ingestion of drugs and also a roentgen examination of the chest.

DR E W NETHERTON I was convinced that this was a good example of a rare dermatosis, known as lichen pilaris seu spinulosus of Crocker, or lichen spinulosus of Devergie. The lesions show the characteristics described by Crocker. In Crocker's cases, there were patches of discrete, uniform sized, follicular papules, with small keratotic spines, which extended well above the surface of the apex of each lesion. The lesions in his cases, as well as in the one presented, occurred on the lateral surfaces of the body, along the axillary folds, and on the upper portions of the arms. The follicular keratotic lesions of lichen planus, as described by Dr DeOreo are usually more erythematous and are associated with typical lesions of lichen planus. We must remember that the lesions in this case have been present for four years. One would expect lesions characteristic of lichen planus to develop in this time. I believe that the small pink lesion on the dorsal surface of the hand and the one on the flexural surface of the right arm are the result of slight trauma. According to Hamilton Montgomery, the histologic changes in lichen planus, of the follicular type, are similar to those seen in lichen spinulosus.

NOTE—Two weeks after the patient was presented before the society, he was seen again. The erythematous lesions on the hand and forearm had disappeared, and there were no lesions on the mucous membrane of the mouth or lips. The other lesions for which he was presented had not changed.

Lichen Planus, Poikiloderma of Civatte Presented by DR G M STROUD

Subacute Disseminate Lupus Erythematosus, Atopic Eczema Presented
by DR R C LIGHT and DR J KAM

Pemphigus Vegetans Presented by DR R C LIGHT for DR H N COLE and
DR J R DRIVER

L L Praver, MD, *President*

G W Binkley, MD, *Secretary-Treasurer*

May 23, 1946

A Case for Diagnosis (Erythroplasia of Queyrat? Granuloma Inguinale?)
Presented by DR B HELD, DR M H GUSTAFSON and DR J BOWEN

Hidradenitis Suppurativa of the Axillas, Inguinal Region and Perineum
Presented by DR B HELD, DR M H GUSTAFSON and DR J BOWEN

Charcot Joint of the Left Shoulder and the Spine Presented by DR B
HELD, DR M H GUSTAFSON and DR J BOWEN

Herpes Gestationis, Pigmented Nevus of the Foot Presented by DR R C
LIGHT and DR J KAM

Dermatitis Medicamentosa (Fixed Arsenical Eruption) Presented by
DR R C LIGHT and DR J KAM

Sarcoid of Boeck, Folliculitis Keloidalis, Late Latent Syphilis Cured
or Arrested Presented by DR R C LIGHT and DR J KAM

Subacute Lupus Erythematosus Presented by DR B HELD, DR M H GUS-
TAFSON and DR J BOWEN

Harley A Haynes, MD, *President*

George W Binkley, MD, *Secretary*

Sept 26, 1946

A Case for Diagnosis (Syphiloderm?) Presented by DR H D POCOCK JR
(by invitation)

H H, a man aged 26, served in the South Pacific from July 1942 to October 1945, during which time he received quinacrine hydrochloride (atabrine®) for malaria. He was discharged from the Army in October. In December crusty pustular lesions developed in the inguinal region, associated with tender inguinal lymphadenopathy. These lesions subsided spontaneously after two weeks, but four similar lesions immediately developed on the penis. A local physician examined smears from the lesions and performed blood tests, the results of which the patient reported as normal. His physician gave a six month course of antisyphilitic therapy consisting of twenty-four intravenous and six intra-muscular injections.

He was admitted to Crile Veterans Administration Hospital on June 24, 1946. Six weeks prior to his admission, similar lesions developed on both knees and multiple dime-sized lesions extended down to both ankles. The lesions were purulent, with crust formation. He was discharged from the hospital on August 8,

after the cessation of the use of the drug, let alone six months later. The presence of quinacrine hydrochloride can easily be demonstrated with the Wood light. If there is any possibility of sensitivity to quinacrine hydrochloride, it is easily found out by giving the patient a small trial dose.

DR H H JOHNSON: I have seen 350 cases of cutaneous reactions to quinacrine hydrochloride and concur with Dr Haynes's statement, and, in addition, I have never seen any which started with sharply delineated ulcerations.

NOTE.—Repeated dark field examinations of material taken from the penile lesions revealed *Treponema pallidum*. The patient received 7,000,000 units of penicillin, which brought about complete involution of the penile lesion and considerable healing of the lesions on the legs.

Late Cutaneous Syphilis (Gumma) Presented by Dr I E RAUSCHKOLB

Lichen Sclerosis et Atrophicus (Submammary and Intergluteal) Presented by Dr J H STRAUCH for Dr H N COLE and Dr I E RAUSCHKOLB

Adenoma Sebaceum with Tuberosus Sclerosis Presented by Dr H H JOHNSON

Dermatitis Herpetiformis. Presented by Dr G A DEOREO, Dr J BOWEN, Dr M GUSTAFSON, Dr B HELD and Dr M UTTERBACH (service of Dr I E RAUSCHKOLB)

Parapsoriasis Varioliformis in a Woman Aged 65 Years Presented by Dr E B HEISEL

A Case for Diagnosis (Gumma? Granuloma Inguinale?) Presented by Dr G A DEOREO, Dr J BOWEN, Dr M GUSTAFSON, Dr B HELD and Dr M UTTERBACH (service of Dr I E RAUSCHKOLB)

Leukemia Cutis Presented by Dr G A DEOREO, Dr M GUSTAFSON, Dr J BOWEN, Dr B HELD and Dr M UTTERBACH (service of Dr I E RAUSCHKOLB)

A Case for Diagnosis (Erythema Induratum, Ecthyma?). Presented by Dr G A DEOREO, Dr M GUSTAFSON, Dr B HELD and Dr M UTTERBACH (service of Dr I E RAUSCHKOLB)

A Case for Diagnosis (Bromoderma) Presented by Dr J BOWEN, Dr G A DEOREO, Dr M GUSTAFSON, Dr B HELD and Dr M UTTERBACH (service of Dr I E RAUSCHKOLB)

A Case for Diagnosis Presented by Dr E B HEISEL

K. E., a white woman aged 25, first noticed redness of the upper half of her right ear in July 1942. At that time she was in the seventh month of her pregnancy. Near the end of her pregnancy she noticed a roughness appearing on the upper third of the red area. After the baby was delivered, it seemed that the redness decreased somewhat, but the surface did not change. The lesion remained in this condition until about March 1945, in the third month of her second pregnancy. In the upper third of the purplish red area there then began to develop small tumor masses, which were soft on palpation and on

several occasions, when she injured the ear, it would bleed freely. This area also became infected and was covered with a soft yellowish brown crust. Near the end of her second pregnancy some redness developed on the tip of the other ear, but, except for some telangiectasis, this has disappeared. Since the termination of her second pregnancy, in October 1945, there has been a slight regression of the process.

Physical examination at the present time shows a diffuse purplish red eruption on the superior half of the lateral surface of the right ear. On the entire area there are numerous telangiectatic vesicles. The superior third of this area is covered by grouped compressible vascular tumor masses. These tumors are purple, except at the anterior portion, where they are almost the color of normal skin. On the surface of this tumor there are some small dilated vessels.

Two specimens were removed for histologic examination. On June 13, 1945, Dr. Wilbur Sachs of New York described a section as follows, "In the center of the section there was a tremendously dilated lymph vessel. About this the tissue was very loose and lacy and there were numerous stellate-shaped cells. The epidermis and adnexa show no important change." His diagnosis from microscopic study was lymphangioma with myxomatous degeneration. On Feb. 5, 1946, another specimen was examined by Dr. H. M. Hartwell of Columbus, Ohio. His description was as follows, "There was a small 'fibroma,' or excess of scar tissue, elevating the epidermis in the center of the tissue. The dermis showed an increased number of sebaceous glands, some containing granular degenerated sebum. The dermal veins were dilated, but no new vessels were seen. There were periaadenitis and perifolliculitis in all areas of the tissue."

Treatment has consisted of application of antiseptic ointments, and on two occasions solid carbon dioxide was applied with moderate pressure for ten to twelve seconds.

DISCUSSION

DR. H. N. COLE: From examination alone, without any history, I made the diagnosis of lymphangiohemangioma. I think that this should respond to roentgen therapy.

DR. H. G. MISKJIAN: I thought of angiolupoid, but I do not believe that the results of biopsy are consistent with it.

DR. E. B. HEISEL: I am especially interested, of course, in the diagnosis, but more in how to treat the patient. I have treated her twice with solid carbon dioxide, and I think that there has been mild improvement. The lesion involves not only the rim of the ear but the upper half of the ear. It was interesting that during both of her pregnancies there was an increase in its size. During the last pregnancy the telangiectatic vesicles on the left ear were much more pronounced.

Parapsoriasis en Plaque Presented by DR. D. R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER

Harley A. Haynes, M.D., President

George W. Binkley, M.D., Secretary

Jan 23, 1947

Superficial Epitheliomatosis of the Trunk Presented by DR. G. A. DEOREO, DR. J. BOWEN, DR. M. GUSTAFSON and DR. M. UTTERBACH from the service of DR. J. E. RAUSCHKOLB

Mycosis Fungoides (Plaques and Tumors). Presented by Dr. G. A. DeOreo, Dr. J. Bowen, Dr. M. Gustafson, Dr. B. Held and Dr. M. Utterbach.

Pemphigus Erythematodes (Sencar-Usher Syndrome) Presented by Dr. G. A. DeOreo, Dr. J. Bowen, Dr. M. Gustafson, Dr. B. Held and Dr. M. Utterbach.

A Case for Diagnosis (Scrofuloderma? Mycotic Infection?) Presented by Dr. G. A. DeOreo, Dr. J. Bowen, Dr. M. Gustafson, Dr. B. Held and Dr. M. Utterbach.

A Case for Diagnosis (Squamous Psoriasiform, Fixed Drug Eruption?) Presented by Dr. G. A. DeOreo, Dr. J. Bowen, Dr. M. Gustafson, Dr. B. Held and Dr. M. Utterbach.

Scurvy Presented by Dr. J. Bowen, Dr. M. Gustafson, Dr. B. Held and Dr. M. Utterbach.

N. W., a white man aged 44, complained of pain in the lower extremities and headache. His diet since 1929 had consisted mainly of corn, bread, and potatoes and occasionally some milk and a little meat.

The patient is pale and lethargic. The gums are swollen and bleed on pressure. The tongue is pale and the teeth erode, and a pale fluid exudes from the gum line. Follicular petechiae are present on the legs and the follicular orifices show keratotic plugging. There is also hemorrhage into the hamstring muscles, the calf muscles and the popliteal space and ankles.

The urine was normal. The erythrocyte count was 2,600,000 with 75 G. of hemoglobin, the leukocyte count was 7,500, with polymorphonuclear cells 77 per cent, lymphocytes 16 per cent, monocytes 2 per cent, and platelets 5 per cent. The platelets were normal. The erythrocytes were hypochromic. The bleeding time was 15 minutes and the clotting time 6 1/2 minutes. The clot retraction was normal. The blood urea nitrogen was 31.9 mg. per hundred cubic centimeters. The albumin was 32 mg. and the globulin 41 mg. per hundred cubic centimeters. The albumin-globulin ratio was 0.78. The serologic test of the blood gave a positive reaction. The vitamin C content in the blood was 0.6 mg. per hundred cubic centimeters on Jan. 21, 1947. No histologic examination was made.

Treatment has consisted of the administration of vitamin C.

Dr. F. McDonald: I accept the diagnosis of scurvy, and I also felt that the patient had a vitamin A deficiency. However, what I found most interesting was the vitamin C level of the blood. In general, the vitamin C level is no indication of the degree of clinical avitaminosis present. Also, low vitamin C levels are found to accompany almost any systemic infection or intoxication and are not indicative of inadequate vitamin C intake. Such patients are not to be expected to benefit from ascorbic acid therapy in any disease except scurvy.

Dr. G. W. Binkley: A hospital resident who became interested in scurvy arranged with the hospital dietitian to receive a diet low in vitamin C while eating in the hospital (Crandon, J. H., Lund, C. C. and Dill, D. B. *Experimental Human Scurvy, New England J. Med.* 223:353-369 [Sept. 5] 1940). After about sixty days of a low vitamin C level in the blood, the first clinical lesions began to develop. This was follicular keratosis, such as is seen in vitamin A

deficiencies After ninety days, when he was about to decide that there was no such thing as scurvy, clinical manifestations of scurvy developed and a biopsy proved the diagnosis

DR H A HAYNES How low was the level and how long did it take the blood level to drop?

DR G W BINKLEY It dropped to a low level within a week to ten days, and it required sixty days for clinical manifestations to become evident

Xanthoma Tuberosum Multiplex of Elbows and Knees Presented by DR J KAM, DR R C LIGHT and DR A E WALKER from the service of DR H N COLE and DR J R DRIVER

Harley A Haynes, M D, *President*

George W Binkley, M D, *Secretary*

Feb 27, 1947

Erythema Annulare Centrifugum Presented by DR HUGO HECHT

V R, an 18 year old white boy, was first seen on Aug 5, 1944, when he was 15 years old He had a skin eruption of four years' duration The patient complained only of a slight itching

The lesions are located on the trunk There were at no time any lesions on the face, hands or feet There are three types of lesions (1) Large, gyrate lesions of different sizes, some of them 15 cc in diameter, with a hard, elevated, erythematous border 5 to 8 mm in diameter The center is composed of normal skin The border later becomes broken, and in due time the entire lesion completely disappears, leaving only slight pigmentation, which disappears also in a few weeks or months, so that no trace of a lesion remains (2) Somewhat smaller lesions, never larger than 2 to 3 cm, which are solid (without a center of normal skin) and resemble lesions of erythema exudativum multiforme The center is somewhat depressed, there are no bullous lesions (3) Some small lesions resembling pityriasis rosea, scaling with the typical frill

This picture has always been the same The patient was seen again in October 1945 and in January 1947

A Case for Diagnosis (Keratosis Palmaris et Plantaris Climacterica, Improved After Treatment with Estrogenic Substance) Presented by DR HUGO HECHT

Syphilitic Gumma of the Scalp Simulating Bromoderma and Blastomycosis Presented by DR G H CURTIS and DR E W NETHERTON

Sarcoidosis Presented by DR B LEVINE, DR I L SCHONBERG and DR B PERSKY

L E C, a Negro aged 19, fell off a bicycle two years ago, bruising his elbows and knees Tumor masses appeared at the sites of trauma One year ago lesions developed on the eyelids, nose and abdomen Six months ago pain developed in his chest, with severe cough, and he expectorated mucopurulent material, but no blood Six weeks ago the glands in his neck became swollen He has night sweats, and his activity is sharply limited because of cough and dyspnea on walking His appetite is good

There is no history of tuberculosis, syphilis or diabetes in the family. He has had atrophy of the right leg, resulting from poliomyelitis at the age of 3. Two years ago he had an operation on his right leg.

Examination revealed fullness and swelling of the parotid region, the cervical lymph nodes and axillary and inguinal lymph nodes. There is decided clouding of the cornea of the right eye, with small, papular, infiltrating nodules. The liver and spleen are enlarged. The reflexes are all present except the right biceps tendon reflex. Spread over both upper eyelids, the bridge of the nose and the fore elbows, abdomen, thighs and penis are flat papules of varying size slightly higher than the surrounding skin.

Roentgen examination showed the bones of the hands and feet to be normal. A roentgenogram of the chest revealed bilateral, symmetric, hilar and paravascular radiating strands into both lung fields. There were nodular shadows along the course of these strands. There was no evidence of cavitation. The observations were typical of sarcoidosis of the lungs.

An electrocardiogram showed a normal tracing. Examination of the blood showed the sugar to be 75 mg, with nonprotein nitrogen 10 mg, total creatinine 0.6 mg, calcium 9.4 mg, phosphorus 3.7 mg, phosphatase 2.5 mg, cholesterol 165 mg, esters 82 mg, icterus index 7 and total proteins 7.3 Gm (albumin 4.0, globulin 3.3). The result of the sulfobromophthalcin sodium test was 45 per cent after 5 minutes, 2 per cent after 30 minutes and 0 after 45 minutes; the serum was clear. The results of Kline slide precipitation tests for syphilis were negative to start with. The spinal fluid was clear, the cell count 1 and the result of the Pandy test 0. Sodium chloride was 600 mg per hundred cubic centimeters, protein nitrogen 4.3 mg and total protein 26.8 mg. There were no pellicles in the fluid. The sedimentation was unsatisfactory because of too little material, and the result of the colloidal gold test was 1112310000. The result of the tuberculin test was negative on two occasions. The blood hemogram was normal. Urinalysis showed a trace of albumin and an occasional coarse granular cast.

A biopsy was done. Section of a lymph node showed the normal structures in great part replaced by miliary granulomatous lesions. In many places the granulomatous lesions were adjacent to each other, but not coalescent. Some of the granulomatous lesions showed fibrinoid degeneration in the central portion. At the periphery there were numerous giant cells of the Langhans type and generous pink-stained material was present, possibly amyloid. There was very little intact lymph node tissue.

Section of the skin showed at one edge miliary granulomatous lesions similar to those seen in the lymph nodes. The lesions were confined to the upper part of the dermis, with the overlying epidermis intact. Elsewhere the skin showed abundant brown pigmentation in the basal layers and slight round cell infiltration in the pericapillary location in the upper portion of the epidermis. In a section of lymph node and skin stained by the Ziehl-Neelsen method no acid-fast bacilli were found. Treatment has been supportive.

DISCUSSION

DR G. A. DE ORO: I think that this case of lymphogranulomatosis benigna is a good example of one of the things Schaumann described—the involvement of glandular as well as cutaneous elements, the right parotid gland and uveal tract seemed to be likewise involved.

Darier's Disease, Improvement After Consumption of Butter but not Vitamin A Capsules Presented by DR B LEVINE, DR I L SCHONBERG and DR B PERSKY

J G, a white man aged 26, lost 8 to 10 pounds (4 to 5 Kg) in the two months prior to the first examination, in 1942. At that time he had considerable pain over the umbilical region and the right lower quadrant of the abdomen. There was also a history of frequency of urination, dysuria and nocturia. Roentgenograms showed hypermobility of the gastrointestinal tract. There was no familial history of contagious diseases.

His present illness began seven years ago, with the presence of pinhead-sized follicular lesions on the back. Examination reveals innumerable pinhead-sized, brownish and erythematous follicular papules, some of which are confluent and encrusted, spread profusely over the upper part of the back, between the shoulders. There is a thickening of the skin over the hyperthenar eminences. There is also a hyperkeratotic scaly process of the scalp.

The hemogram and urinalysis revealed no abnormalities. The result of the Kline precipitation test was negative.

A biopsy specimen showed the histologic picture of Darier's disease.

The patient was treated with a keratolytic ointment. He was given vitamin A capsules of 25,000 units and thyroid, 1 grain (65 mg) three times daily. At first there was moderate improvement. Later, after using 225,000 units of vitamin A per day, he showed no further improvement. However, the condition virtually cleared after the patient ate 2 pounds (907 Gm) of butter a week over a period of eight months. The use of margarine had no effect. The patient is allergic to almost all fruits except pineapple, bananas, grapefruit, lemons, limes and strawberries, he is also allergic to nuts.

Morphea Guttata (Lichen Sclerosis et Atrophicus of Clavicular Regions)
Presented by DR BENJAMIN LEVINE

Lichen Sclerosis et Atrophicus, Widespread on Neck, Trunk, Vulva and Folds of the Body Presented by DR G H CURTIS and DR E W NETHERTON

A Case for Diagnosis (Macular Eruption Apparently Due to Allophen® [Contains Aloin, Extract of Belladonna, Ipecac and Phenolphthalein])
Presented by DR G H CURTIS and DR E W NETHERTON

Syphilitic Superficial Sclerosing Glossitis, Neurosyphilis Presented by DR G H CURTIS and DR E W NETHERTON

Chronic Pemphigus, of One Year's Duration Presented by DR E L GLICKSBERG

Xanthoma Tuberosum Multiplex Presented by DR B PERSKY

Necrobiosis Lipoidica (No Evidence of Diabetes) Presented by DR E W NETHERTON and DR G H CURTIS

DISCUSSION

DR E W NETHERTON: I should like to report a case of xanthoma tuberosum in a Negro boy. I had 2 cases in which the use of phosphatides recommended for psoriasis caused the xanthoma to disappear almost miraculously. I have thought

of treating the boy with soy bean lecithin. It is unbelievable how rapidly the lesions regressed. The patient presented today shows the numerous, small lesions seen in xanthoma disseminata. There are some more recent preparations which might be tried in this case.

Actinomycosis (*Nocardia Asteroides*) Presented by DR. E. W. NETHLRIEN and DR. G. H. CURTIS

E. S., a Mexican laborer aged 48, has had an eruption involving the left hand and wrist since 1929. He ran a thorn into the left palm while working as a laborer in Michigan. A small pustule developed at the site of the injury and a portion of the thorn was removed. The lesion never completely healed. A year after the injury, the patient removed a foreign body. However, instead of healing, the pustule continued to discharge. Gradually new lesions appeared on the palmar dorsum of the hand and the volar and dorsal surfaces of the wrist. During the past year the lesions have become decidedly more numerous, accompanied with thickening and limitation of motion of the wrist. Recently there has been pain on use of the wrist.

Roentgenograms of the left hand and wrist showed no involvement of the joints or bones. Typical radial clubbing of granules was identified in the sputum. On culture, the organism was found to be aerobic and grew well on Sabouraud's medium, with an irregular folded surface and light pink color.

Microscopic study of the fungus showed it to consist of clusters of delicate short mycelia. The organism was acid fast and gram-positive. The fungus was identified as *Nocardia asteroides*. The principal features in the macroscopic sections of a nodule from the skin consisted of a large area of subcutaneous inflammation not encapsulated, but which contained a high degree of edema, fibroblastic proliferation and an infiltrate of polymorphonuclear cells, lymphocytes, plasma cells and eosinophils. There were several small abscess foci, one of which contained encapsulated fluid. The epidermis overlying the area of inflammation was thin. The organisms in the section stained with polychrome methylene blue appeared as reddish-purple, granular masses in the abscess foci.

The patient has been receiving treatment since April 1946. Treatment has consisted of roentgen therapy, potassium iodide and sulfadiazine. Sulfur granules and positive cultures have been repeatedly obtained throughout the course of the treatment.

DISCUSSION

DR. E. W. NETHLRIEN: This organism is aerobic whereas actinomycosis is anaerobic. We grew this on brain broth the first time. The first time the patient was seen, numerous small nodules could be demonstrated and took a stain which is characteristic of *Nocardia asteroides*. The cultures have lost that acid-fast property. We are going to put it back on the original culture. The patient has responded well to sulfadiazine, with some roentgen treatment. Sulfonamide drugs are preferable to penicillin.

LOS ANGELES DERMATOLOGICAL SOCIETY

Clement E Counter, M D , *Chairman*

Maximilian E Obermayer, M D , *Secretary*

April 9, 1946

Localized Scleroderma Presented by DR FRANKLIN I BALL

A A , a girl aged 13, five years ago noticed the appearance of small discolored spots on both flanks, they have enlarged to their present size, and additional lesions have appeared on the back, close to the spinal column. The lesions are sharply outlined, ovoid plaques, ranging from the size of a half-dollar to that of a palm, which follow the lines of cleavage and are symmetrically distributed. There is a moderate degree of induration. The lesions are somewhat depressed, and some of the more recent ones have a faint violaceous areola.

Hemograms and results of urinalyses were normal, and Wassermann reactions of the blood were negative. Microscopic examination showed thickening of the corium by dense, undulating, refractile connective tissue fibers. A slight lymphocytic infiltration was present immediately beneath the basal layer and about the adjacent vessels.

DISCUSSION

DR ANDREW G LIGHTER I could not see one single lesion typical of scleroderma or morphea. I could not detect induration in any lesion. In the presence of many lesions of different ages, one would expect induration in at least some if it were a case of scleroderma. The typical yellowish-brownish waxy hue of scleroderma is also missing. The discoloration is rather that of hyperpigmentation. If I have to accept the diagnosis of scleroderma at all, I should say that the lesions are residual rather than reactive. But in this case the disease is not inactive, for new lesions have recently appeared. Incidentally, the patient has also follicular hyperkeratotic changes which resemble those of mild keratosis pilaris or lichen spinulosus.

DR L H WINER (by invitation) Clinically this eruption looks like scleroderma, but, as Dr Lighter said, palpation discloses no induration. The microscopic section shows in places thinning, atrophy of the epidermis and thickening of the dermis. However, one expects a thick corium in specimens for biopsy from the back. Sebaceous glands are present. I am at a loss for a definite diagnosis. There is definite atrophy and hyperpigmentation. Special staining of sections to show changes in the connective tissue is in order. This is a form of atrophy but not scleroderma.

DR J WALTER WILSON (by invitation) Two sections were presented, one an old biopsy specimen, and the other a recent one. In both there is a great deal of hemosiderin. Some hemorrhagic process should be considered in differentiation.

DR FRANKLIN I BALL I have presented this case as one of localized scleroderma, for lack of a better classification, and I feel that this is the most

likely diagnosis. The thing that makes me hesitate to make this diagnosis definite is the presence of pigmentation, noted particularly in the older lesions. I wonder whether the other members were able to observe the faint violaceous areolae surrounding some of the newer lesions. I believe that there is a moderate degree of induration in the newer lesions. I think that the patient has morphoea of a mild type in which there are spontaneous resolution of the lesions and residual pigmentation.

Generalized Progressive Scleroderma Associated with Pronounced Muscular Dystrophy. Presented by Dr. SAMUEL AYERS II

DISCUSSION

DR W. H. GÖCKERMAN: Over the years, in discussions with dermatologists and neurologists, I have obtained varied opinions as to whether dermatomyositis is a distinct disease or is part of the scleroderma syndrome. Neurologists are interested particularly in the muscular atrophies and dystrophies which are laid to the central nervous system and their relation to scleroderma. There is no doubt that in some cases of scleroderma the muscles are only lightly involved, while in others muscular involvement predominates. This case illustrates the fact well and throws considerable doubt on the concept that dermatomyositis is a distinct entity. It is interesting that a number of such patients who were on the verge of destruction recover with only a moderate residual, either as the result of treatment or, seemingly, spontaneously.

DR L. H. WINER (by invitation): This case is a classic example of diffuse scleroderma. Atrophy of the muscles of the pectoral and the scapular region and the paravertebral muscles is strikingly evident. When the patient bends over he cannot straighten up again unless he pushes with his arm, braced against his thighs. I have never seen a patient with scleroderma diffusum who displayed as much muscular atrophy as this man. The involvement of the fingers has caused sclerodactylia, but there is motion of the elbows. His mouth looks almost like a fish mouth. No microscopic section was available. This case shows the close relation of scleroderma diffusum and muscular atrophy.

Nevus Pigmentosus. Presented by Dr. ARTHUR K. JENSEN

L. E., a Caucasian woman aged 30, has had a darkly pigmented, slightly elevated, pea-sized lesion on the left cheek, 2.5 cm. below the eye, since birth. During the last year it has enlarged until it now measures about 1 cm. in length by 0.5 cm. in width. The more recent part of the lesion is lighter brown and is level with the surface of the skin. The lesion has not been treated nor has a biopsy been made.

DISCUSSION

DR FRANKLIN I. BALL: It is my belief that in the case of a pigmented hairy nevus which is showing signs of activity, as evidenced by change in the character of the pigmentation and growth or spread of the area of pigmentation, microscopic study is needed to determine the diagnosis. I believe that this lesion should be excised widely and considered probably malignant until the diagnosis is established histologically.

DR H. P. JACOBSON: Despite the history of enlargement, close inspection of the lesion shows no evidence of activity suggestive of malignancy. By this

I mean that there is no scaling, erosion, fissuring or other change in the surface markings and no induration. Consequently, since the lesion is located on the face of a young woman, I should be reluctant to recommend surgical intervention at this time. The surgical handling of hyperpigmented lesions suspected of malignancy means radical excision, and such surgical procedures imply extensive scarring and disfigurement. I believe that the conservative course of observing the patient for a limited period of weeks is indicated at present.

DR J R SCHOLTZ I should like to ask Dr Jacobson three questions: 1. What are the signs of activity in lesions of this type? 2. Is it not true that lesions with a history such as this has are more likely to become malignant eventually than lesions without such history? 3. Is it not true that in many instances metastasis may occur before there are signs of activity in the initial lesion?

DR M E OBERMAYER I am surprised at Dr Jacobson's remarks. He who has repeatedly cautioned about the danger of potential melanomas advises an expectant attitude in the case of a blue nevus which has become definitely enlarged during the past year. I am equally unable to understand Dr Scholtz's point of view, expressed in the remark that one should wait for signs of activity. What additional proof of activity can one expect? The mere fact that a blue nevus has recently changed its shape is sufficient grounds for one's considering the lesion a potential or actual melanoma. I wish to go on record with the statement that the only permissible procedure in this case is speedy surgical excision of the lesion, including 1 cm of the apparently healthy margin and the subcutaneous fatty layer.

DR H P JACOBSON I fully agree with Dr Obermayer's and Dr Scholtz's observations about the lesion's being potentially malignant. The potentiality is there, but clinical evidence is definitely lacking today. In reply to Dr Scholtz, I may state that I have yet to recall a single instance of melanoma in which metastasis became manifest prior to the showing of malignant activity by the primary cutaneous element.

DR SAMUEL AYRES JR I think that it is a cardinal principle that when a black mole starts to change it is time to take action, whether the change consists in the lesion's becoming inflammatory, larger, deeper or more elevated. It will not be any easier to perform an operation later than it is now. I do not believe that the preservation of feminine good looks should be allowed to warp clinical judgment. Also, suppose that the specimen does not show malignancy, at least it will have been removed before there is any possibility of disaster.

DR THOMAS STERNBERG (by invitation) It seems to me that patients with a lesion of this sort, if presented, should be labeled "do not touch." The prognosis is doubtful at best, and it is certainly not improved through palpation by 40 or 50 persons.

DR A FLETCHER HALL I believe that there might be a compromise. Those who talk about excising widely and deeply never say how wide and how deep. One presumes that they mean cut down to fascia and widely enough to include about ten times the diameter of the lesion, if it is small. I should like to supplement Dr Jacobson's remarks on the lack of evidence of activity with two points: 1. The original part of this lesion is black, and the new region is brown, not vice versa. Moreover, the dark portion of the lesion has not become more tense, those lesions I have seen which were manifestly malignant had a

ago I should like to suggest that this patient be followed up, without additional treatment, until it is definitely established that the cutaneous lesions are not going to heal. If they do not heal and the results of the dark field examinations become positive, I suggest that he be given 80,000 units of penicillin every three hours for fifteen days, for a total of 9,800,000 units. Failure to respond to this dosage of penicillin would be a rare phenomenon well worth reporting.

A Case for Diagnosis (Trichophytic Granuloma with Bullous Lesions?)

Presented by DR. M. E. OBERMAYER and DR. J. WALTER WILSON

A Case for Diagnosis (Granuloma Annulare?) (Sarcoid of Boeck?)

Presented by DR. A. FLETCHER HALL

A Case for Diagnosis (Acquired Epidermolysis Bullosa?)

Presented by DR. A. FLETCHER HALL

DISCUSSION

DR. ANKER K. JENSEN: I treated a patient with a severe recurrence of epidermolysis bullosa with testosterone propionate. Within a week all lesions had completely cleared up except for one area on the extensor surface of his right arm.

Nevus Unius Lateris, Keratotic Type ("Ichthyosis Hystrix")

Presented by DR. A. FLETCHER HALL.

Erythema Annulare Centrifugum

Presented by DR. A. FLETCHER HALL

Clement E. Counter, M.D., Chairman

Maximilian E. Obermayer, M.D., Secretary

May 14, 1946

Neurosyphilis Amyotrophic Lateral Sclerosis

Presented by DR. HAROLD E. ANDERSON

Combined Ectodermal and Mesodermal Defect Hand-Schuller-Christian Syndrome

Presented by DR. HAL E. FREEMAN

S. S., a girl aged 2 years and 9 months, has never been healthy. Her skin has always had a yellow tinge. The eruption was noticed in the mouth at the age of 3 months, an axillary abscess appeared at the age of 6 months and an eruption on the scalp, the ears and the chest at 9 months. Bilateral mastoidectomy was performed. There is considerable pruritus, especially at night.

The child looks sallow and rachitic, and her forehead is prominent. There is a pustular and crusted eruption on the scalp, "scutuloid" in appearance, and an erythematous-vesiculo-pustulo-follicular eruption on the chest, the back and the ears. An oozing and erythematous dermatitis is present in the axillae, especially the right. The posterior cervical lymph nodes are enlarged, and several large soft areas are present in the frontal and parietal regions of the skull.

Urinalyses in 1945 disclosed that the specific gravity ranged from 1.004 to 1.008, the most recent value is 1.024. Examinations of the blood have revealed 3,700,000 to 4,300,000 erythrocytes and 10,900 leukocytes, the hemoglobin content has ranged from 10.8 to 11.1 Gm. Culture of material obtained at mastoidectomy yielded *Staphylococcus aureus*.

A cranial roentgenogram disclosed several large areas of decreased density, especially in the frontal region, which gave the appearance of "geographic skull"

Treatment has consisted of mild local applications, sodium salicylate given orally, high voltage roentgen therapy (190 r three times) to the posterior region of the pituitary and superficial fractional roentgen therapy to the involved cutaneous areas

DISCUSSION

DR NELSON PAUL ANDERSON I think that it is remarkable that the names of Hand, Schuller and Christian are attached to a disease the essential nature of which they did not know. The three merely described patients with eruptions and defects of the membranous bones associated with diabetes insipidus. I did not inquire whether this girl has the latter condition. I do not think that the child has an ectodermal defect, but rather a primary essential xanthomatosis or the Hand-Schuller-Christian syndrome. The defects of the bones of the skull and the peculiar erosion and loosening of the teeth suggest that this same process involved the mastoid region. Those who are familiar with the otologic literature will know that in a considerable group of cases the disease was discovered by otologists after performing a mastoidectomy. In addition, this patient has something which I do not believe has been associated before with this syndrome, namely, tinea amiantacea, a peculiar scaling of the scalp which I think is primarily a streptococcic infection. I should advise the presenter not to be discouraged, because I think that most patients with this disease have responded to radiation, particularly as far as the cranial lesions are concerned. If the xanthomatous infiltrate does not involve any vital spot the prognosis may be fair, although it must always be guarded.

DR MOLLEURUS COUPERUS This is a classic example of Hand-Schuller-Christian disease. Last year I had a 6 month old patient with this same disease who had the same seborrheic type of eruption and, in addition, the purpuric lesions which have also been described in this entity. My patient succumbed to the disease after a couple of months, typical foam cells were found in many of the internal organs on microscopic examination.

DR SAMUEL AYRES JR. I wonder whether some of the cutaneous manifestations might be associated with vitamin A deficiency. Some of the lesions on the chest suggested Darier's disease. I wonder whether the changes on the scalp have a similar basis and are complicated by associated secondary infection.

DR HAL E. FREEMAN The syndrome is characterized by a tetrad: defects of the flat bones, diabetes insipidus and exophthalmos. Roland, in 1928, suggested that the disease is a xanthomatosis. About a third of the patients die, those who survive may be dwarfed as a result of the pituitary involvement. This patient had high voltage roentgen therapy to the posterior lobe of the pituitary, and the diabetes insipidus, at least, has been controlled. Defects in the cranial bones are more commonly encountered than exophthalmos and diabetes insipidus. The cholesterol content of the blood is supposed to be normal. One case has been reported in which use of a high fat diet caused most improvement. Lane, in 1939, reported 3 cases which terminated fatally. In each lipoidosis was evident, and in each the large mononuclear cells known as xanthoma cells were identified. In 1941 Cornbleet and Barnes suggested that the tetrad of Hand-Schuller-Christian disease actually represents three entirely separate and distinct entities and that this syndrome should not be considered a lipoidosis. Since my patient has both dermatitis and a mesodermal defect (bone), it occurred to me that the condition could be called a mesodermal and ectodermal defect. Less than one third of the

patients who present the triad have cutaneous manifestations. Often cutaneous xanthomas are present, but this patient had none. I do not agree with Dr. Anderson that the dermatitis of the scalp is tinea amiantacea. The dermatitis, to me, is not asbestos-like but scutula-like. However, I think that everyone will agree that it is entirely seborrhea-like.

Seborrheic Dermatitis? Psoriasis? Moniliasis? Presented by DR. ANKER K. JENSEN

Urticaria Pigmentosa in a Girl Aged 2 Presented by DR. MAXIMILIAN E. OBERMAYER

DISCUSSION

DR. NELSON PAUL ANDERSON: Some years ago I read a note by Dr. Lester Hollander on urticaria pigmentosa of the acquired adult type, in 2 or 3 cases he found a greatly enlarged thymus gland. The mother of this patient recalls that when the child used to nurse she became blue around the lips. I think that it might be well to take a roentgenogram of this child's chest, to see whether anything like a persistent thymus is present.

DR. J. WALTER WILSON: I was interested in the microscopic section, in which Dr. Winer was able to demonstrate the presence of mast cells without the usual special staining.

DR. M. E. OBERMAYER: I presented this case merely to show that most textbooks err in stating that the infiltrate is composed of dense rows and columns of mast cells. Often one finds only a few mast cells in the section, and I remember 1 case in which such cells were absent. The object of administering diphenhydramine hydrochloride (benadryl®) was simply to have the inefficacy of this mode of therapy recorded. I thank Dr. Nelson Paul Anderson for his suggestion, I shall obtain a roentgenogram of the chest.

A Case for Diagnosis: Chronic Ulcers of the Arm (Factitious?) Presented by DR. NELSON PAUL ANDERSON

Noduloulcerative Syphilid, Sporotrichosis? Tularemia? Presented by DR. MAURICE N. NORRIS

Actinomycosis (Arrested) Presented by DR. NELSON PAUL ANDERSON

A Case for Diagnosis: Infectious Granuloma? Presented by DR. A. FLETCHER HALL

A. B., a woman aged 58, consulted a physician in October 1945 regarding a small growth inside the left nostril. It was incised, and soon after lesions began to appear on and around the nose and spread to the upper lip and the cheeks. The nose became enlarged and partially obstructed, and edema of the lower eyelids developed. The patient has lived in the San Joaquin Valley for many years.

The nose, up to the narrowest part of the bridge, is covered with pale to light purplish smooth nodules from the size of a pinhead to that of a pea. The alae and septum are thickened and indurated. The left side of the upper lip, including the mucocutaneous junction, is covered with nodules, a few of the larger lesions show superficial ulceration. The cheeks are erythematous and are also studded with nodules, the lesions at the periphery are pale pink and rubbery in consistency. The lower eyelids are edematous.

The Eagle and Kline reactions were negative, and the differential blood cell count was normal

Microscopic examination of a specimen from the right side of the nose showed areas of necrosis in the lower part of the dermis surrounded by an infiltrate consisting of fibroblasts, small lymphocytes, epithelioid cells and occasional giant cells. No yeast cells were seen.

The patient was treated for rosacea, by another physician, with fractional roentgen therapy and penicillin ointment, there was no improvement.

DISCUSSION

DR M E OBERMAYER Clinically the plaque presented all the features of a chronic infectious granuloma, yet its duration was said to be only five months. With the exception of a late syphilid, there is no chronic infectious granuloma which within such a brief period would produce a plaque with such clinical characteristics. I am inclined to interpret the eruption as bromoderma simulating a chronic infectious granuloma.

DR SAUL S ROBINSON I should be inclined to call this a case of tertiary syphilis. I should apply the therapeutic test for syphilis and report later.

DR NELSON PAUL ANDERSON I should suggest that Dr Hall do a coccidioidin skin test and send blood to Dr Smith, at Stanford University, for an agglutination test.

DR HAL E FREEMAN Those procedures would not establish the diagnosis. Many people who live in the San Joaquin Valley have positive reactions to coccidioidin and agglutination tests, this granuloma may have some other cause.

DR HAROLD C FISHMAN (by invitation) Dr C E Smith has expressed the belief that unless the disease is active there will not be a positive reaction to an agglutination test. For instance, patients who have had lesions in the past which cleared up and who still react positively to coccidioidin skin tests will not show positive reactions to complement fixation or precipitin tests unless there is some activity of the disease.

DR A FLETCHER HALL I saw this patient first one week ago. Since she lives in Stockton, coccidiomycosis immediately came to mind, but because no coccidioidin was available in Santa Monica I depended on biopsy to disclose any organisms which might be present. However, rather thorough search of three slides showed no organisms. I shall certainly do coccidioidin and tuberculin tests, and I shall also obtain a roentgenogram of the chest.

Kraurosis Vulvae? Presented by DR J WALTER WILSON

A Case for Diagnosis Lenticular Parapsoriasis? Lymphoblastoma?
Presented by DR PAUL D FOSTER

H B, a German-Irish woman aged 51, noticed the appearance of itching spots on her ankles about two and a half years ago, and soon similar lesions appeared on her arms. The eruption has been continuously present, although individual lesions come and go. Firm pea-sized violaceous papules are present on the arms, legs, hands and upper part of the back.

Urmalysis gave normal results. The differential blood cell count, the blood sugar, the nonprotein nitrogen content of the blood and the sedimentation rate were also normal. The Wassermann reaction was negative. Microscopic examination showed in the dermis a heavy polymorphous infiltrate which included

some large nucleated cells Treatment has consisted of injections of bismuth subsalicylate in oil, desensitizing injections of flea antigen, the administration of asiatic pills, fractional roentgen therapy and ultraviolet irradiation

DISCUSSION

DR L H WINER (by invitation) I do not consider parapsoriasis en plaque a precursor of mycosis fungoides Clinically this patient does not appear to have a malignant disease Histologically one is astounded by the cellular infiltrate which involves the entire cutis except for a small band directly under the epidermis Since this infiltrate abounds in large cells with large nuclei suggestive of reticulum cells, the picture is compatible with the diagnosis of mycosis fungoides This eruption suggests parapsoriasis clinically, but histologically it looks like mycosis fungoides

DR M E OBERMAYER Through the courtesy of Dr Foster I had the opportunity to study this patient before the meeting The eruption impressed me as the nonvarioliform type of pityriasis lichenoides acuta of Haberman The striking clinical features of the lesions of which such an eruption is composed are their induration and color, which always bring both a lenticular syphilid and "bites" from *Climax lectularius* to my mind Study of the microscopic section, however, revealed a cellular infiltrate unusual in its polymorphism for Haberman's disease I do not feel that a definite diagnosis can be made at this time If the eruption is the nonvarioliform type of acute parapsoriasis, it may clear up without treatment in from six months to two years, if it is granuloma fungoides, more definite development of the disease will undoubtedly take place

Lupus Erythematosus, Subacute, with Tendency to Dissemination Presented by DR HARRY P JACOBSON

A Case for Diagnosis Dermatitis Venenata? Epidermolysis Bullosa Acquired Type? Presented by DR H C L LINDSAY and DR OTTO P HANNEBAUM (by invitation)

A D, an Italian man aged 50, five weeks ago spilled a strong solution of washing powder on the back of his hands, it burned, but he did not wash it off A few days later blisters appeared on the dorsa of the hands, ruptured and formed scabs One week later lesions appeared on the nose, the forehead and the back of the neck The original lesions healed within a few days, but new crops appeared, this process was repeated three times His wife stated that the skin of his face has become darker

There are several dental cavities and pyorrhea The skin is darkly pigmented A vesicobullous eruption is present on the dorsa of the hands Most of the lesions are pea sized, have indurated bases and contain a yellowish red fluid Several larger bullae are located on the wrists and thumbs Many crusts and recently cleared areas are seen Patch tests with the washing powder solution gave no reaction within forty-eight hours

The differential blood cell count was normal The Kolmer and Kline reactions were negative Microscopic examination showed the presence of a bulla filled with serum-like material between the epidermis and the dermis, minimal inflammatory changes, in the form of slight endothelial swelling and perivascular lymphocytic infiltration, were also noted Treatment has consisted of injections of chorionic gonadotropin (antuitrin S®), fractional roentgen therapy and mild local applications

DISCUSSION

DR SAMUEL AYRES JR I think that this patient has pemphigus and Addison's disease. The striking deep brownish tone to his skin, he says, is recent. The lesions are limited to his hands and might suggest an acquired type of epidermolysis bullosa, but in view of the bronzing of his skin I should be willing to bet that true pemphigus will develop. The association of adrenal damage and pemphigus has been discussed recently. I never encountered pemphigus associated with Addison's disease until about a month ago, the patient died. Autopsy revealed severe adrenal damage. I think that this diagnosis deserves careful consideration and that some adrenal cortical extract should be administered.

DR FLORALOU KETTENBACH I should suggest a search for porphyrins in the urine.

DR M E OBERMAYER Is it not possible that this patient simply has bullous impetigo? The eruption has been present only five weeks, and it is limited to the hands. Some lesions show peripheral inflammation, and there is one large pustule. The hyperpigmentation of the skin may only be apparent, since the patient is of southern Italian stock. I should like to see impetigo ruled out by a therapeutic test with penicillin ointment.

DR MAURICE N NORRIS I think that the lye splashed on the patient's hands has given rise to chemical burns, which have become secondarily infected.

DR L H WINER (by invitation) The histologic appearance of the lesions is most suggestive of epidermolysis bullosa or pemphigus, the bullae are not as superficially placed as in impetigo contagiosa. The bullae are subepidermal. The blisters of impetigo contagiosa involve only the stratum corneum, they never go below the granular layer. I favor a diagnosis of epidermolysis bullosa.

DR M E OBERMAYER I feel that Dr Winer's remarks on impetigo were meant to apply to the streptococcal type of the disease. The lesions of staphylococcal impetigo have thicker walls, are more deep seated and show no tendency to rupture. Thus impetigo in this case is by no means ruled out by the fact that the lesions are not superficial.

DR H C L LINDSAY As a rule the lesions of pemphigus do not appear on sites subject to trauma. Most of the lesions of this patient are on the fingers and hands. The blebs of pemphigus are not as flaccid as those of epidermolysis bullosa. Some lesions were slightly tinged with blood. I believe that the original diagnosis of epidermolysis bullosa acquisita is correct.

DR OTTO P HANNEBAUM (by invitation) When this patient was first seen I thought that he had suffered a chemical burn from the solution used in his work as a window cleaner. The bullae were opened, and he improved, but since then he has had four more crops of bullae, and those on the forehead and neck could not be due to chemical injury. I still believe that this patient has epidermolysis bullosa, and steps are now being taken to determine the porphyrin content of the urine.

Coccidioidal Granuloma, Results Beneficial from Immunogenic Therapy

Presented by DR HARRY P JACOBSON

A Case for Diagnosis, Lymphoblastoma? Toxic Nodular Dermatitis?

Presented by DR. HARRY P JACOBSON

J G, a man aged 40, was hospitalized nine years ago for several weeks because of fever and pain in the chest. Roentgenograms showed infiltration of

the left pulmonary apex, but repeated examination of the sputum failed to yield evidence of tuberculous infection. Recently he had a cold and sore throat and has been coughing somewhat the past few weeks. Twelve or thirteen years ago a cutaneous eruption developed. The initial lesion was a scaly inflamed patch on the external aspect of the right thigh, and shortly thereafter the eruption spread, in the form of plaques, to various parts of the body. At various times since the dermatologists in Cincinnati and New York have made a diagnosis of psoriasis. His blood has been examined several times, with uniformly normal results. About a week ago a tense vesicular lesion, about 7 mm in diameter, developed on the dorsum of the right wrist. Culture mediums were inoculated with the fluid, which was evacuated under aseptic conditions, but no growth resulted. Within forty-eight hours the site of the bulla had changed into a nodule.

The patient is well developed. His tonsils are injected, especially the left one. Also present is gingivitis in the region of the lower left cuspid.

On the trunk and extremities there is an extensive eruption, made up of bright to dusky red, variously sized and shaped nodular elements in variously shaped and sized patches, discrete and grouped. Some lesions have scaly collarets as well as scaly surfaces, but none shows evidence of ulceration. On the cutaneous surfaces of the lower thirds of the thighs and the knees, especially the right, are dark, intensely pigmented, scaling patches, with here and there a nodular element. The pigmented patches are perceptibly indurated.

The blood cell count was within normal limits. The sedimentation rate was 3 mm in 15 minutes, 10 mm in 30 minutes, 19 mm in 45 minutes, 27 mm in 60 minutes, and 49 mm in 120 minutes. The Kline and Eagle reactions were negative. Hemolytic and nonhemolytic staphylococci were cultured from material from the nose and nonhemolytic streptococci and staphylococci from material from the throat. Stereoscopic roentgenograms of the chest disclosed no abnormality.

Microscopic examination of lesions on the right side of the thoracic wall and the lower part of the left thigh showed an extensive diffuse infiltration in the dermis, made up of a pleomorphic conglomeration of cells which included eosinophils, a few neutrophils, small round cells and occasional plasma cells and larger cells which had irregularly lobular and slightly vesicular nuclei. Some cells of the last type contained several nuclei. A few showed mitotic figures, and a few were hyperchromatic.

DISCUSSION

DR L. H. WINER (by invitation). I should suggest a diagnosis of eosinophilic granuloma, which is closely allied to the lymphoblastomas. I have read reports in which this diagnosis was reached after surgical removal of tumors and studies of the bone marrow. I have seen similar lesions previously which were called lymphoblastomas for want of a better term. The microscopic section is packed so densely with eosinophils that one might think they make up the whole section. I should say that this disease is not as malignant as such other forms of lymphoblastoma as Hodgkin's disease and mycosis fungoides.

Psoriasis, Generalized, with Extensive Oral Lesions Presented by DR THOMAS W. NISBET

Linear Scleroderma (en Coup de Sabre) of the Back of the Neck in a 10 Year Old Boy Presented by DR H. C. L. LINDSAY and DR OTTO P. HANNEBAUM (by invitation)

A Case for Diagnosis: Granuloma Annulare? Presented by DR. L F X WILHELM and DR. W H GOECKERMAN

The futility of trying to differentiate clinically or histologically, granuloma annulare and erythema elevatum diutinum was discussed

Epidermolysis Bullosa, Acquired Type, in a 21 Year Old Woman. Presented by DR. SAMUEL AYRES JR.

Neurodermatitis? Presented by DR. J WALTER WILSON

Nevus Cerebriformis of the Scalp in a 14 Year Old Boy Presented by DR. SAMUEL AYRES JR.

Acne Conglobata Arrested by the Use of a Specially Prepared Autogenous Vaccine. Presented by DR. H P. JACOBSON

A Case for Diagnosis, Lupus Vulgaris? Presented by DR. ANKER K. JENSEN.

There was no agreement about the diagnosis

A Case for Diagnosis: Lupus Erythematosus? Presented by DR. H P JACOBSON

There was no unanimity of opinion about the diagnosis

Dermatitis Herpetiformis in a Patient Who Did Not Tolerate Sulfapyridine. Presented by DR. BEN A. NEWMAN

Ichthyosis Hystrix Presented by DR. A FLETCHER HALL

Pigmented Purpuric Lichenoid Dermatitis of Gougerot and Blum Presented by DR. SAMUEL AYRES JR.

Lichen Planus et Spinulosus in a 10 Year Old Girl Presented by DR. H C L. LINDSAY and DR. OTTO P. HANNEBAUM (by invitation)

Maximilian E. Obermayer, M D, *President*

Franklin I. Ball, M D, *Secretary*

Oct 8, 1946

A Case for Diagnosis (Nevus or Localized Scleroderma) Presented by DR. CLEMENT E. COUNIER.

A Case for Diagnosis (Acne Conglobata, Infantile). Presented by DR. SAMUEL AYRES JR.

G. H., a 26 months old white boy has an eruption of the face of about five weeks' duration. Two symmetrically placed lesions appeared first on each cheek, followed later by two similar symmetrically placed lesions below each lower eyelid. The history reveals that this patient also apparently had a mild acne-like eruption at the age of 1 month which lasted for several weeks

Physical examination shows this child to be a normal healthy-appearing boy. On the center of each cheek is the remnant of a former lesion which is purplish and scarlike. Beneath each lower eyelid is a red cherry-seed-sized slightly fluctuant swelling, with a suggestion of pus in the center. A few tiny comedos can be seen in the face. At the time of the first visit, on Sept 19, 1946, lesions beneath the eyes were incised, with evacuation of purulent material. These lesions have filled again with similar material.

On September 18 a blood cell count showed red blood cells 5,300,000, white blood cells 13,900, color index 0.67 and hemoglobin 11.0 Gm (71 per cent). The platelets were apparently normal in number, the red blood cells were moderately hypochromatic, anisocytotic and poikilocytotic. The differential count was neutrophils 38, stab forms 4, lymphocytes 4, monocytes 4 and eosinophils 4. A culture of material taken from lesions revealed *Staphylococcus albus*.

Treatment administered to date includes incision and drainage of purulent lesions and two intravenous injections of vaccine.

DISCUSSION

DR J. R. SCHOLTZ: I recently saw an infant of 9 months of age who presented acne-like lesions which had been present since the age of 1 month. Definite comedos were present and a number of milium cysts. Inasmuch as acne is essentially a disease of adolescence or, at least, is often associated with endocrine disturbance, it seems to me that acne in an infant should not be passed off lightly without careful investigation. My patient, whom I saw only once, was large for his age, having large bones, head and genitalia, the liver was large, and there was a disturbed cholesterol ester ratio. I have no information on the progress except that he is receiving roentgen treatment in another dermatologist's office. The patient presented here shows few comedos, but there are intradermal milium cysts on the cheeks in addition to the inflammatory lesions on the eyelids. I would agree with Dr. Ayres' diagnosis as presented. That infantile acne is not a minor disturbance is illustrated by the fact that adrenal tumors develop in many cases. The most recent reference was in the proceedings of the New England Dermatological Society (*ARCH. DERMAT. & SYPH.* 54:82 [July] 1946).

DR NELSON PAUL ANDERSON: I think that it is necessary first to determine whether this patient has acne. The patient had one or two lesions on the cheeks and recently one on the lower lid, reddish and granular in character. I would suggest an aberrant type of pyoderma or molluscum contagiosum.

DR SAMUEL AYRES, JR.: I have never seen a picture quite like this. The patient does have a few comedos. With good light one could easily distinguish two, three, or four small comedos scattered on the face. The lesions are not actually on the eyelids. They are on the cheeks beneath the eyelids. They develop in pairs. At the time of the first visit the lesions beneath the eyelids were found to contain pus, similar to that in deep acne lesions. The child has rather pronounced secondary anemia, which may have something to do with the picture, and is now being treated for that. In reply to the question of other cases of acne in infants, I have seen 6 or 8 patients in twenty-six years with typical acne, but not this deep cystlike involvement. In 1 or 2 that I was able to follow the acne disappeared. I have never treated infantile acne with roentgen rays. It might be justifiable, but only in an extreme case. Feeling that the patient has a sensitivity to *Staphylococcus*, I prepared an autogenous vaccine and, pending results, I gave him some *Staphylococcus* vaccine intravenously, prepared

from another patient. The lesions today are considerably less inflamed than they were a week ago. I do not know whether this is due to treatment with vaccine, to the iron therapy or to a coincidence. The eruption may result in serious deformity if allowed to continue. The reason I have given vaccine intravenously is based on some work by Blanson and Allen done eight or ten years ago. They studied patients with arthritis to whom they were giving vaccines, and on the basis of some careful tabulations they expressed the opinion that a greater degree of immunity was achieved by intravenous therapy and that sometimes tissues were made more hypersensitive by subcutaneous than by intravenous therapy. I have given autogenous vaccines intravenously in cases of acne conglobata and recurrent furunculosis when I felt that there was a sensitivity of the tissues, and I have never seen any untoward effects except a slight febrile reaction. It seems to give good results.

DR H P JACOBSON. Dr Ayres' point is well taken. I have employed the intravenous routes for immunogenic therapy for a number of years and have been impressed by its effectiveness. Intravenous antigenic therapy provides a rapidly circulating antigen capable of evoking specific immune bodies in all tissues able to produce immune bodies—such as precipitins, agglutinins and globulins. The most important tissues in the production of these immune bodies are the cutaneous and peritoneal. For an immunogenic antigen to reach these important immunity-producing organs, the route of administration is extremely important. The first, and possibly the second, injection of a vaccine will exert immunogenic functions regardless of the site of injection—cutaneous, subcutaneous, intramuscular or intravenous—except, of course, for the speed of absorption, which varies inversely according to the choice of route enumerated. The effect of succeeding injections, however, is limited by the element of tissue anchorage and inflammatory reaction in situ, which must be given due consideration. Thus, successive immunogenic antigen administrations via the cutaneous-subcutaneous route meet in due time with a most pronounced barrier to passage into general circulation through phagocytic action of the mobile as well as the fixed tissue cells, and probably globulin, precipitin and agglutinin action, and frequently by a simple inflammatory reaction in situ which serves to destroy the immunogenic antigen. In the intramuscular route, however, the element of anchorage is not nearly as pronounced and the vaccine is almost as rapidly absorbed by the general circulation, therefrom transmitted systemically to a satisfactory degree.

The most effective route with respect to speed of absorption and intended destination of the antigen is, of course, the intravenous channel. However, in view of the occasional shocklike systemic reactions which I have observed in intravenous antigenic therapy, and in view of the fact that the intramuscular route, as just mentioned, almost approaches the intravenous route in effectiveness, I have lately been employing this avenue for the administration of vaccines and am satisfied that in the great majority of instances this is the most desirable method available.

DR SAMUEL AYRES JR. It has been my observation that if one gives a *Staphylococcus* vaccine intravenously a beginning dosage of 25,000,000 will not produce an untoward reaction. If one uses a *Streptococcus* vaccine I would say that a beginning dose of a 250,000 would be proper. In the infant, the first dose was 5,000,000 and the second dose 10,000,000 with no untoward results.

DR H C L LINDSAY. In 1913, Colonel Alcott, who was in Dr Metchnikoff's department of the Pasteur Institute, was using vaccine intravenously, and

he claimed that he obtained wonderful results. When in England, I told Dr Henry Macormac (of the Middlesex Hospital) about this type of treatment. He expressed the opinion that it was dangerous. I have seen some of the patients Dr Ayres has treated here, and the results have been both spectacular and useful.

DR L. H. WINFR. The characteristic deep pustules localized to the follicular and sebaceous apparatus are suggestive of pyoderma faciale. Chronic pyoderma can become pyoderma vegetans.

A Case for Diagnosis (Lymphoblastoma?) Presented by DR H. C. L. LINDSAY and DR O. P. HANNFBAUM (by invitation)

Epidermodysplasia Verruciformis (Lewandowsky-Lutz) Presented by DR NELSON PAUL ANDERSON

E. S. W. is a housewife, white, aged 31. This case was the first example of epidermodysplasia verruciformis reported in this country and was first presented before this society in April 1934 as a case for diagnosis (*ARCH DERMAT & SYPH* 30 731 [Nov] 1934). In October 1934, the patient was again presented before this society with a tentative diagnosis of epidermodysplasia verruciformis, a diagnosis with which Goeckerman agreed (*ARCH DERMAT & SYPH* 31 369 [Feb] 1935).

At the time of the first presentation, she had numerous discrete rather widely dispersed flat papular lesions on the dorsa of the feet and the backs of the hands. There were also a few lesions on the sides of the neck. These lesions were of five years' duration, beginning at the age of 14.

After a lapse of twelve years, this patient is again presented. During this interval the patient married and gave birth to one healthy child showing only several verruca vulgaris lesions on the dorsum of the right hand. At the present time, the patient presents a striking picture, with hundreds to thousands of lesions fairly widely disseminated over the entire body. In many places the lesions are discrete, erythematous to brownish, fairly flat topped and papular. Elsewhere a pseudolichenification has appeared, because of a fusion or blending of these papular elements. About the neck, there is a striking clinical similarity to Darier's disease. Because of this clinical similarity to Darier's disease, she was given large doses of vitamin A on Aug 7, 1946. At the present time there has been a definite improvement.

Epidermodysplasia Verruciformis (Lewandowsky-Lutz) Presented by DR NELSON PAUL ANDERSON

M. V. R., aged 34, a white woman secretary, for the past fifteen years or more has had numerous solitary and grouped erythematous and flat-topped papular lesions on the dorsa of the fingers and thumbs, with a few scattered verruciform lesions on the palms.

Cases have been presented by Weber before the Chicago Dermatological Society (*ARCH DERMAT & SYPH* 49 216, 1944), by Ricchinti before the Atlantic Dermatologic Conference (*ARCH DERMAT & SYPH* 49 365, 1944) and by Wise before the New York Dermatological Society (*ARCH DERMAT & SYPH* 50 228, 1944).

The patient presented by Wise was the original patient of Sullivan and Ellis (Sullivan, M. and Ellis, F. A. *Epidermodysplasia Verruciformis* [Lewan-

dowsky and Lutz], ARCH DERMAT & SYPH **40**:422 [Sept] 1939) At the time of the presentation, Wise stated that his patient had five different and fairly large epitheliomas of the face and hand Some were basal cell in character and others of a prickle cell type He stated that he knew of 2 other cases of this rare disease in which epitheliomas had developed

Laboratory examination of a section from a biopsy specimen reveals a peculiar balloon degeneration or vacuolization in the epidermis, which is most evident in the granular layer There is the so-called basket weave appearance of the overlying thickened horny layer This picture was considered to be entirely different than that of acrokeratosis verruciformis (Loveman, A B, and Graham, O V Acrokeratosis Verruciformis [Hopf], ARCH DERMAT & SYPH **43** 971 [June] 1941) and typical of epidermodysplasia verruciformis as described by Wise and Satenstein (Epidermodysplasia Verruciformis [Lewandowsky-Lutz] ARCH DERMAT & SYPH **40** 742 [Nov] 1939) and by Waisman and Montgomery

Darier's Disease (Unilateral) Presented by DR NELSON PAUL ANDERSON

S H S, aged 53, a white man, a minister, for the past fifteen years or more has had a unilateral eruption involving the right side of the neck, the right side of the trunk, where the eruption has a definite segmental linear arrangement, and the lower part of the right ankle The past history shows that the eruption flares up during hot weather, especially if it is humid Laboratory examination of a section from a biopsy specimen reveals definite and typical Darier's disease

DISCUSSION OF CASES OF DR ANDERSON

DR L H WINER (by invitation) The first patient, the woman, had diffuse verrucous lesions on the dorsum of the hands associated with lesions on the neck and anterior axillary folds I agree with the presenter's diagnosis of acrokeratosis of Hopf and also agree with the diagnosis in the second case, that of the girl with the lesions on the thumbs The histologic section was typical of epidermodysplasia verruciformis of Lewandowsky and Lutz I think that both diseases are closely related and may be the same They are to be differentiated from verrucae planae The histologic differentiation is difficult The only differentiating characteristic is that in verrucae planae the acanthotic epidermis forms a sort of convex mass on the upper part of the cutis, whereas in the nevroidal conditions there is papillomatosis as well as acanthosis If this were present in verrucae planae the disease would be verruca filiformis Interesting was the association in the third case of Darier's disease with acrokeratosis In virus diseases in which there are benign dyskeratoses, for example, Darier's disease, verrucae vulgares, psoriasis, chickenpox and smallpox, one observes these nucleolar and nuclear extrusions The condition in the third of these cases could be most readily diagnosed *nevus unius lateris* However, histologically, it is Darier's disease, in that lacunas, corps ronds and grain cells are present

DR. J R SCHOLTZ Several years ago, I reported a case to this society with the diagnosis of Darier's disease, and at that time Dr Anderson, on the basis of the histologic section, without having seen the patient, made the diagnosis of epidermodysplasia verruciformis At that time, I had not yet seen a case of this disease I would like to speak briefly about the importance of vitamin A in dermatologic therapy To me this is one of the most important therapeutic aids which has been made available in recent years My co-workers

and I have demonstrated to our own satisfaction that 200,000 units given daily over a period of several months will cause the disappearance of the keratoses which occur in senile skin, in chronic actinic dermatitis and in related conditions. This means that it will prevent cancer. For this reason alone, it is of tremendous importance. In vitamin A therapy, however, it is essential that certain facts be kept in mind, for example, vitamin A is a fat and in some persons may not be properly absorbed because of conditions in the bowel or gall-bladder, and it may be necessary to give bile salts at the same time. On the other hand, if carotene is given, some persons may not convert carotene to vitamin A, as, for example, in the presence of thyroid deficiency. This last point may be of importance in connection with the treatment of acne. It is therefore essential to realize that simply giving vitamin A or carotene may not, in fact, be effective treatment unless other factors are taken into consideration. Therefore, one must not conclude that vitamin A is not effective in conditions such as Darier's disease or epidermodysplasia verruciformis until one is sure that it has been given in its most effective way.

DR J WALTER WILSON: What is the distinction between the Lewandowsky and Lutz syndrome and verrucae planae of the hands? I was impressed by the fact that some of the lesions in the cases of less extensive involvement would simply pass as tiny verrucae planae, which are frequently seen. What would happen if such lesions as these were curetted and treated with trichloroacetic acid? Would they recur?

DR NELSON PAUL ANDERSON: I agree with Dr Winer that the third patient undoubtedly has Darier's disease. What relationship, if any, exists between this disease and epidermodysplasia verruciformis is unknown. I have been impressed by the literature of this disease, in which Dr Fred Wise of New York has made such excellent observations that he has knowledge of 3 cases in which epitheliomatous degeneration has occurred. I do not believe that Darier's disease is considered to be a precancerous condition. In 1 of Dr Wise's cases there developed five epitheliomas on the face and one on the back of the hand. Some were basal cell and some were prickle cell in character.

I think that Dr Winer became a little confused in his terminology. There is another of these keratotic conditions which affects the extremities, called acrokeratosis verruciformis of Hopf, which is not the same as epidermodysplasia verruciformis of Lewandowsky and Lutz. The only paper on that subject in English was written by Loveman of Louisville, Ky. In his paper he told of lesions on the neck of his patient which were histologically identical with those of Darier's disease. The disease might be regarded possibly as some sort of a nevroid condition in which different types of keratotic lesions are present rather than that such lesions are related. Apparently the keratosis verruciformis of Hopf does have a different microscopic picture than epidermodysplasia verruciformis. Dr Hamilton Montgomery and Dr Waisman have written an excellent article on the differentiation of verrucae planae, epidermodysplasia verruciformis and allied conditions. It might be of interest to read the closing discussion of Dr Montgomery, in which he said that they were unable to review personally any of the cases, the diagnoses were made from the histologic files, and the lesions had been diagnosed as verrucae when the patients were at the Mayo Clinic.

Dr Wilson asked about the differentiation between flat warts and epidermodysplasia verruciformis. They are difficult to differentiate histologically. Most dermatologists do not remove flat warts for histologic examination. One

can examine all of the articles in this country on this subject, and the only article to give a photomicrograph of the histologic appearance of flat warts is that of Montgomery. The fact that the lesions in the Lewandowsky-Lutz type of eruption apparently have never been spread by autoinoculation is the final and definite criterion. As far as therapy is concerned, I have tried electro-desiccation without a great deal of success. I have 3 or 4 patients with this disease in a mild degree, some with only five or six lesions. Most of these patients are treated by dermatologists for flat warts. The second patient was treated by me with that diagnosis until I made a more careful examination. The case of unilateral Darier's disease is the only case of its kind I have ever seen. I am indebted for both the diagnosis and the excellent histologic section to Dr. Manson of Richmond, Va.

A Case for Diagnosis (Localized Light Sensitization Following Injury by a Yucca Plant?). Presented by DR. A. FLETCHER HALL

A Case for Diagnosis (Pemphigus of the Mouth?). Presented by DR. SAMUEL AYRES JR.

Maximilian E. Obermayer, M.D., *President*

Franklin I. Ball, M.D., *Secretary*

Nov. 12, 1946

Acne Followed by Keloids (Severe). Presented by DR. SAMUEL AYRES JR.

DISCUSSION

DR. MOLLEURUS COUPERUS: I have never seen a reaction to acne vulgaris to duplicate this condition. This case is a real therapeutic problem. I would favor the use of filtered roentgen rays on these areas, believing, however, that not too much help can be expected from any form of therapy in this keloidal reaction.

DR. A. FLETCHER HALL: The fact that hypertrophic scars followed acne vulgaris while they did not follow vaccination and several other wounds occurring in the same patient makes one wonder what causative factors are operative. I have seen similar scars follow varicella, when the child was covered with hundreds of hypertrophic scars, smaller but similar to these. The facial scars were individually shielded and treated with subintensive doses of roentgen rays; they subsided while the untreated body scars did not. I believe that at one of last year's meetings of this society, Dr. Obermayer called to our attention the effects of use of sodium fluoride internally in the treatment of keloids. I believe that where there are as many lesions as in this case, a trial of this treatment would be indicated before an attempt is made to shield and treat each scar separately. I have never seen satisfactory results follow fractional roentgen therapy, such as could be given without shielding.

DR. H. C. L. LINDSAY: A few years ago a German, Cadam, reported using 1 per cent aqueous solution of sodium fluoride for treatment of keloids. The dose was 5 to 10 minims (0.31 to 0.61 cc.) given on an empty stomach three times a day (*Munchen med Wchnschr* 38:1554 [Sept.] 1935). I tried this treatment in a patient with keloid and obtained a good result.

DR. M. E. OBERMAYER: May I call your attention to the experimental work on keloids by Marshall? He claimed satisfactory response to the tumors to local

injections of special fractions of liver abstract which were prepared for the purpose by Eli Lilly and Company and are not commercially available, the vasoconstricting action of that fraction was said to be responsible. In this patient, however, there are not keloids alone, but an active inflammatory process with keloidal tendencies. The object of therapy would therefore be primarily cessation of the patient's acne vulgaris and only secondarily the management of the accompanying keloids. Nevertheless, it would be of interest to see whether the internal administration of a 1 per cent aqueous solution of sodium fluoride might not change the keloidal tendency of the disease. I believe that from the use of the substance in appropriate dosage (from 1 to 3 drops three times daily in a full glass of water before meals) no untoward reactions will occur.

A Case for Diagnosis (Lymphoblastoma? Drug Eruption?) Presented by DR. MOLIEURUS COUPERUS

Squamous Cell Epithelioma (Self-Healing Type) Presented by DR. SAMUEL AYRES, JR.

G. A. B., a white man aged 63, presents a lesion on the left temple which first appeared about four and one-half months ago. At the time he reported for observation, it had apparently reached a stationary stage but was typical of a squamous cell epithelioma with a hard, less than dime-sized, elevated nodule, showing a typical rough, warty-looking surface. At the same time, he presented a typical squamous cell epithelioma on the back of the left hand which he thought was already beginning to subside. Inasmuch as this patient has been under observation at intervals since 1925 and has had a number of epitheliomas about the face of both squamous and basal cell types, some of which have been observed to retrogress without treatment, and inasmuch as the present lesions were apparently stationary, it was decided to carry out no treatment for the present. Specimens of tissue from each lesion proved them to be squamous cell epitheliomas. The lesion on the hand, however, showed evidence of increasing activity, and it was destroyed widely and deeply by means of the high frequency cutting current. About a month later, two new lesions developed on the back of the hand, one on either side of the wound from the previous lesion, in spite of the fact that an ample margin had been removed at the time of the operation. These lesions were also removed surgically by means of the high frequency cutting current and, at the present time, the lesions on the hand have nearly healed. In the meantime, the lesion on the left temple, which received no treatment, has continued to recede until at present it is practically flat and barely visible.

DISCUSSION

DR. L. H. WINER: The patient has multiple lesions on the face and ear. Those that healed did so with a depressive scar. There was follicular plugging in the active lesions. Rather than epithelioma, this suggested the diagnosis of lupus erythematosus clinically. The histologic section shows the proliferation of epithelium that one sees in pseudoepithelioma. There is no keratinization present. The epidermis is acanthotic, but the section has been cut obliquely. The infiltration suggests that these may be pseudoepitheliomatous hyperplasia in lupus erythematosus. I can see where the proliferating epidermis gives this appearance, but I do not believe in the spontaneous cure of cancer, and I do not believe that this is a squamous cell carcinoma. From a clinical point of view, I think that this is pseudoepitheliomatous hyperplasia.

DR KENNETH L. STOUT I thought that histologically the lesion did show keratinization. However, there was one point which would favor pseudoepitheliomatous hyperplasia over prickle cell epithelioma, and that was the leukocytic infiltration, not only in the cutis but also in the proliferating epithelial portions. The leukocytes were principally eosinophils.

DR W. H. GOECKFRMAN This is a most unusual case. I cannot conceive, on biologic grounds, that a carcinoma could disappear spontaneously, then recur, disappear and recur again. However, there is rarely a spontaneous cure of cancer. In 1924, I reviewed the literature thoroughly and critically, and it was difficult to escape the conviction that certain rare cases do heal spontaneously. But the behavior of the lesion in this case, if it is carcinoma in the biologic not morphologic sense, which I doubt much, is unique.

DR NELSON PAUL ANDERSON I made the diagnosis of grade I or II prickle cell carcinoma, I have never seen pseudoepitheliomatous hyperplasia in lupus erythematosus. I do not believe that this is pseudoepithelioma as is seen in bromoderma, syphilis and the like. Histologically there was a grade I prickle cell epithelioma characterized entirely by epithelial whorls and pearls. One could make no other diagnosis, and yet the lesions had disappeared spontaneously on several different occasions. I think that the lesions which this patient has had on his face from time to time were definite clinical and histologic prickle cell epitheliomas. In the literature, although rare, there are definite instances of prickle cell epitheliomas of the skin which have healed spontaneously.

DR F. AKRAWI (by invitation) My co-workers and I often see these epitheliomas in Iraq, because the people expose themselves more to the air and sun, but I have never seen any squamous cell epitheliomas heal spontaneously. If some of them do heal in the center, there is always left an active part at the periphery.

DR A. FLETCHER HALL In view of the disagreement between the histopathologists in this society as to whether the microscopic section shows epithelioma or pseudoepitheliomatous hyperplasia, I would not presume to hazard an opinion, but if this is the latter, it must be preceded by some other entity, which I do not believe to be lupus erythematosus. In this circumstance, I suggest the possibility of factitial lesions followed by pseudoepitheliomatous hyperplastic reaction. The peculiar regularity in the size, shape and distribution of the scars and the Mona Lisa-like attitude of the patient suggest such a diagnosis.

DR SAMUEL AYRES JR I have observed this patient since 1925. He appears every two or three years with a lesion which is getting out of control, or occasionally just to show me how one is regressing. The scars that are present are the result of cautery removal of lesions which became active and showed no tendency to heal. The scars were not produced by any manipulations on the part of the patient. Recently a lesion developed on the back of the hand and on the left temple. These lesions were photographed, and biopsy was done. The one on the hand, however, continued to develop rather actively, and it was removed widely and deeply by means of the high cutting current. A few weeks later a new lesion appeared on either side of the wound, and these were also removed widely and deeply. I do not see how I could have left any malignant tissue at the first operation, and I trust they were not metastases. Neither of these lesions looked anything like lupus erythematosus, although the one on the temple might suggest that tonight because it has completely flattened down. Both lesions were typical prickle cell epitheliomas with rounded inflammatory borders and warty-looking centers. Recently there was a paper on the treatment of an epithelioma by injec-

tions of spleen and other tissue extract Apparently some such biologic phenomenon takes place in this patient, which causes the disappearance of some of his lesions while others get out of control I would be interested if anyone has any ideas as to investigative procedures that would utilize the clue which this patient apparently offers

Keratosis Palmaris et Plantaris (Acquired) (Vitamin A Deficiency?) Presented by DR HIRAM D NEWTON (by invitation)

Granuloma Annulare (Extensive, Disseminated) Presented by DR JOSEPH I MIROVICH

Maximilian E Obermayer, M D , *President*

Franklin I Ball, M D , *Secretary*

Dec 10, 1946

A Case for Diagnosis (Parapsoriasis? Angioma Serpiginosum?) Presented by DR MAURICE N NORRIS

A Case for Diagnosis (Cheilitis? Photosensitivity? Lupus Erythematosus?) Presented by DR H C L LINDSAY and DR O P HANNEBAUM

A Case for Diagnosis (Erythema Multiforme Type Lesions Due to Toxic Foci? Pemphigus? Epidermolysis Bullosa Aquisita? Eruption Due to Drugs?) Presented by DR H C L LINDSAY

A Case for Diagnosis (Erysipelas Perstans Faciei?) Presented by DR WALTER F SCHWARTZ

C B D, a white man aged 22, suddenly experienced an acute inflammation of the skin on the face three and a half years ago when, as a student in Iowa, he worked over an acid bath The process developed to its full extent at the onset There is no seasonal variation, in fact, a severe exposure to the sun six months ago did not aggravate the condition There is pronounced flushing and engorgement of the area, lasting only a few days from time to time No subjective symptoms are observed The condition never entirely clears Examination shows diffuse bluish red engorgement deep in the skin on the central part of the face, involving the nose, adjacent cheek areas and extending to the sides onto the temporal regions, the lower part of the forehead and the upper lip The skin blanches with pressure There is a spongy feel, but no increase in skin temperature, and there is no scaling

Histologic examination of a deep biopsy specimen from the right temporal region showed, in sections transversely through the tissue, some thinning of the epidermis with a moderate decrease in the number of the cells of the malpighian layers The under surface of the epidermis is devoid of rete pegs About some of the blood vessels there is moderate round cell infiltration, and in occasional parts considerable numbers of round cells are present A similar infiltrate is present about a hair shaft Occasional sweat glands are still present, and a rare sebaceous gland is included in the sections The greater part of the dermis shows little change There is no evidence of any neoplasm No treatment has been given

DISCUSSION

DR W H GOECKERMAN I would hesitate to make a diagnosis of erythema faciei perstans largely because it almost presupposes a fatal reaction This boy did not impress me as being in that particular phase Persons with such a condition, of course, sometimes look well, but he seems to be rugged When he mentioned that he had been working with plutonium, I examined him carefully He told me he was involved in that work before he experienced this trouble One wonders whether some radioactive rays may be involved

DR J R SCHOLTZ The most striking morphologic feature was the sharp line of demarcation under both eyes It did not involve the lids I could not conceive of an ordinary rosacea with such a line of demarcation The patient stated that he does not wear glasses at any time I am interested in Dr Goeckerman's suggestion that this lesion may have been based on some little known type of radiation I wonder whether the patient wore protective glasses at work Examination of the histologic section certainly is consistent with lupus erythematosus There was extensive follicular plugging, with masses and columns of lymphocytes and some basophilic degeneration I would have been satisfied with the diagnosis of lupus erythematosus

DR WILLIAM MULVEHILL From the histologic picture, I think that one can readily call this lupus erythematosus It has patulous follicles with characteristic lymphocytic filtrate along the hair follicles and blood vessels Erythema perstans is now considered to be a form of disseminate lupus erythematosus

DR M E OBERMAYER I thought that this patient had a seborrheic type of dermatitis perhaps complicated by sensitivity to light and an element of rosacea He gave a history of having recurrent "pimples" on his face, a feature not seen in erythema perstans faciei but suggestive of rosacea His obviously good state of health prevented me from considering acute lupus erythematosus Nevertheless, after having studied the section, I was forced to admit that the eruption is lupus erythematosus, but I do not believe that the patient has the acute form of the disease

DR WALTER F SCHWARTZ The man originally came to me for another complaint and casually asked me for an opinion of the process on his face When he asked me for my diagnosis, he was so impressed by my silence that he readily consented to a biopsy I have seen him when his face was absolutely engorged, the delineation was visible across the room and the lesion had a spongy feel A biopsy was made, and, as has been suggested tonight, lupus erythematosus was the diagnosis, but I could not see this in the clinical picture No scaling and no aggravation by severe exposure to sunlight make it difficult to associate the clinical with the pathologic observations From a clinical point of view, I thought that I would find some peculiar type of hemangioma Kaposi described erythema perstans faciei as a disseminated type of lupus erythematosus, and as yet I have not been able to establish this

Subacute Disseminate Lupus Erythematosus (Favorable Response to Iodine Therapy) Presented by DR. WALTER F SCHWARTZ

Nevus Epitheliomatocylindromatosus (Epithelioma (?) Clinically) Presented by DR KENNETH L STOUT and DR CLYDE O WOOD

Acrodermatitis Chronica Atrophicans, Nodular Type with Facial Involvement Presented by DR. MAXIMILIAN E OBERMAYER

Thrush, Persisting for Fifteen Years Presented by DR BEN A. NEWMAN

H S., white girl aged 15, presents an illness which dates back to the age of 6 months, when an acute inflammation of the mouth with severe edema developed. At this time, she was a patient in the Los Angeles Children's Hospital and the diagnosis of thrush was made. Since then she has had persistent lesions of the oral mucosa. Treatment had been continuous until three or four years ago and included methylrosaniline chloride given locally, curettage and copper sulfate administered locally, vitamins of all types, given orally and parenterally and liver extract. She was presented at this society five years ago with the same condition.

Physical examination shows the entire oral mucous membrane except the dorsal surface of the tongue and hard palate to be covered with a thick milky white membrane, flaky and patchy in appearance so that it resembles exfoliating mucosa. Some of these membranous patches are easily detached, and others are fairly firmly attached to the underlying tissue, so that on forceful separation, there is profuse bleeding. The general physical condition of the patient is good, the blood cell count and urine were normal, repeated cultures on Sabouraud's medium gave prompt growth of *Monilia albicans*.

DISCUSSION

DR J. WALTER WILSON: I believe that there should be some evidence of tissue invasion before a diagnosis of "thrush" is warranted. This is usually manifested by tenderness, ulceration, pain and the presence of bleeding points when a portion of the monilial "membrane" is removed. This patient has had none of these manifestations at any time, and I believe that the proper diagnosis is saprophytic moniliasis. It is possible to obtain cultures positive for *Monilia albicans* from the mouth, intestinal tract and genitalia of many apparently normal persons, and many probably harbor the organism for years. The dividing line between saprophytic and pathogenic monilial infestation is difficult to draw. The factors which cause the development of the disease in the presence of this organism in some persons while not in others are not well known. It seems probable that deficiencies in some of the vitamin B factors may be partially responsible, notably riboflavin and adenylic acid. I believe that local chemotherapy would not be successful in any large number of cases such as this one, and such attempts might cause breaks in the continuity of the membranes sufficient to allow pathogenic invasion.

DR R. W. HELMS (by invitation): I would like to suggest the possibility that this is a nevroid condition, in view of the fact it has been present all the child's life. If it were moniliasis of the mouth, I think that there would be some reddened eroded areas in the mouth and involvement of the tongue. About the culturing of *Monilia*, one can find that in the normal mouth. I wonder whether Sabouraud's agar or cornmeal agar was used. Sabouraud's agar would reveal only a monilial organism. On cornmeal agar one could see the usual wavy growth and on culture mount find terminal chlamydospores if the organism present is *M. albicans*.

DR BEN NEWMAN: This patient was completely studied in the past, and at the Mayo Clinic the organism was found in the lesions.

DR R. W. HELMS (by invitation): I would call it a leukoplakia-like verrucous lesion of the mouth—possibly the white sponge nevus of the mucosa.

DR MOLLEURUS COUPERUS This is an exceedingly interesting condition. I took a tongue blade and scraped the inside of the cheek. The mucous membrane was beefy red and not normal. I could not believe that this was a saprophytic invasion. I agree with the diagnosis of the presenter.

DR J WALTER WILSON I believe that this is a saprophytic process involving the entire intestinal tract. The organism can probably be cultured from stool specimens as well as from vaginal smears. It is entirely possible that cultural studies will prove the presence of *M. albicans* of potential pathogenicity. The fact remains that no disease has been demonstrated. I was one of the early examiners, and I could see no erythema even after removing a bit of membrane. The patient has never complained of discomfort, she said that she is conscious of the condition only by constantly chewing small sections of the membrane from her cheek.

MANHATTAN DERMATOLOGIC SOCIETY

E W Abramowitz, M D, *President*

Wilbert Sachs, M D, *Secretary*

March 12, 1946

Melanocarcinoma with Metastases Presented by DR MAURICE J COSTELLO

T M, a woman aged 50, stated that she had observed a match-head-sized, non-hairy, black mole on the dorsal aspect of the right great toe in her adolescence. This showed no change until a hysterectomy was performed three years ago, the lesion then began to increase in size, and when it was first observed by me on Feb 12, 1945, it had grown to about eight times its original dimensions. The lesion was elevated, coal black and sharply circumscribed, and a reddish brown warty excrescence was observed in its center, distal to which was a fissure. There was enlargement of the inguinal lymph nodes. The lesion was excised by a surgeon in February and a skin graft performed. In September of that year a crescent-shaped, match-head-sized, jet black, satellite malignant melanoma was observed on the cuticle of the right great toe nail, which has increased in size. Recently a serous fluid has exuded from it.

Histologic examination by a general pathologist showed that the lesion was a malignant melanoma, "relatively benign." An enlarged node can be palpated in the right groin at present.

The patient has had chronic pulmonary tuberculosis for many years, but has been able to work at a gainful occupation without interruption since she was "cured" fifteen years ago.

DISCUSSION

DR FRED WISE The only therapy I can suggest is amputation of the toe and removal of the enlarged lymph node.

DR HERMAN SHARLIT No one can say where to begin or end the surgical treatment. I had a case of this kind in which I recommended amputation of the toe, three years later the patient had generalized melanocarcinomatosis.

DR MAX SCHEER I would recommend roentgen therapy.

DR WILBERT SACHS The node should be removed to see whether it is metastatic. If it is, I do not believe that anything can be accomplished, but if it is not I would suggest amputation.

DR ANTHONY C CIPOLLARO I am pessimistic about the eventual outcome of patients with melanocarcinoma. However, those who perform radical surgical procedures report encouraging results. By and large, the prognosis is grave.

DR ISADORE ROSEN I agree with those who believe that the node in the groin should be removed first to see whether it shows metastasis. Often these conditions are only of an inflammatory character.

DR GEORGE C ANDREWS I did not see the patient, but I agree with Dr Sachs that it is wise to remove the lymph node and examine it before one determines the kind of treatment. A roentgenogram of the chest should also be taken. In regard

to Dr Cipollaro's remarks, I presented a patient before this society who had a melanoma of the glans penis. That tumor was removed and grown in tissue culture, and the tissue cultures were implanted and grown into a second tissue culture. It was shown to be an embryonic type of tumor.

DR. MAURICE J. COSTELLO. When I first saw the patient for this disease, she presented a lesion which was about half-dime sized on the dorsal surface of the right great toe. The melanotic mole from which it arose had been present since childhood. It began to increase in size after a hysterectomy. This might well have been coincidence, but nevertheless it offers argument for speculation. The surgeon excised the lesion and replaced it with a skin graft. The procedure was decided on by him because the pathologic report concluded with "melanocarcinoma, relatively benign." In addition, the patient had pulmonary tuberculosis of the quiescent fibrotic type, and the surgeon concluded that the enlargement of the right inguinal lymph nodes was due to secondary infection. The latter conclusion was, in a measure, an accurate one, because lymphadenitis completely disappeared after the lesion on the toe was excised. Recovery was uneventful until six months ago, when a black speck developed on the outer aspect of the nail fold. The surgeon now intends to amputate the toe and remove the femoral and inguinal lymph nodes which have become enlarged again. A roentgenogram of the lungs shows no metastases to these organs. The surgeon hesitated in this case because of the pathologist's report and the presence of tuberculosis of the lungs.

NOTE.—Since the patient was presented before this society, the affected toe has been amputated, and twelve of the fourteen lymph nodes excised showed metastatic melanoma. One cannot help concluding that either an extensive operation should be performed as soon as the diagnosis is made in cases of malignant melanoma or the patient should not be disturbed at all.

A Case for Diagnosis (Tuberculosis Miliaris?). Presented by DR. DAVID BLOOM

Subacute Disseminated Lupus Erythematosus Resembling Psoriasis. Presented by DR. ISADORE ROSEN

Nevus Flammeus. Presented by DR. ANTHONY C. CIPOLLARO

A. R., a girl aged 15, has had an eruption involving the entire left lower extremity since birth. There has been no special change in the disease since it first appeared. Recently she has had swelling of the affected extremity and pain when she stands. There appears to be shortening and a deformity of the involved leg, the greater part of which is involved in a light purplish nonelevated lesion. There are no cutaneous changes other than the discoloration.

DISCUSSION

DR. DAVID BLOOM. The left leg seems to be longer than the right. Besides the nevus flammeus on the left, there are also varicosities, which may be assumed to be the cause of her pain when she stands.

DR. FRANK C. COMBES. I would not be surprised if the lesion were more extensive than it appears. I think that the venous sinuses suggest that, and I wonder whether there is any evidence of sinuses on the labia majora. The lesion may extend all the way into the pelvis.

DR WILBERT SACHS I have seen a few cases of this condition, and the diagnosis was diffuse capillary angioma. It may be arterial rather than venous. There are small foci of capillaries. One patient had elephantiasis due to this type of nevus.

DR GEORGE M LEWIS I think that we are jumping to conclusions. There is no evidence that the varicosities are connected with the nevus flammeus. It is possible and probable, but some obstruction above should also be considered which might be causing the varicosities.

A Case for Diagnosis (Tuberculid?) Presented by DR MAX SCHEER

E W Abramowitz, M D, *President*

Wilbert Sachs, M D, *Secretary*

April 9, 1946

Iododerma, Parotitis and Incipient "Iodism" Presented by DR GEORGE M LEWIS

E A, a white man aged 52, was first seen this afternoon with a widespread polymorphous eruption, moderate soreness and swelling of the parotid glands and slight mental confusion. The eruption was accompanied with moderate pruritus on the body and considerable pain and distress in the face. The patient had been taking strong iodine solution for six months. Lesions were first noted on the abdomen in mid-February, with development of new areas of involvement on the face, neck, back and extremities during the next few days. The parotid swellings and the mental confusion were of more recent onset, while the diffuse involvement of the face followed the application of a lotion containing phenol.

Scattered over the body are numerous purplish red and slightly elevated coin-sized lesions, with evidence of previous central bullous formation. There are many perifollicular hemorrhagic lesions on the thighs. There is a diffuse eczematoid dermatitis on the face and neck. The parotid glands are slightly enlarged.

DISCUSSION

DR ISADORE ROSEN It is interesting to see a patient who has definite eruption due to iodides. This is suggested clinically by the follicular and pustular character of the lesions. When patients are taking several drugs at the same time, all of which may produce cutaneous eruptions, such as the barbiturates, iodides and bromides, it is important to recognize the one which is responsible for the manifestations in the skin.

DR MAX SCHEER I doubt whether the mental confusion is due to iodides. Of course it occurs in bromism, but I do not recall having seen a case of mental confusion from iodides.

DR THEODORE ROSENTHAL (by invitation) The generalized eruption, together with enlargement of the parotid gland, brings to mind the parotitis that occurs in secondary syphilis. Dr Chargin and I studied a case of parotitis associated with a generalized syphiloderm (*ARCH DERMAT & SYPH* 24 236-246, [Aug] 1931), and at first glance there were many clinical similarities to this case. Of course laboratory studies, together with the appearance of the eruption, would rule out syphilis in this case.

DR WILBERT SACHS I was under the impression that iododerma with hemorrhagic bullous lesions is frequently associated with renal involvement.

DR E W ABRAMOWITZ Facial, pharyngeal and intraoral edema and swelling of salivary and thyroid glands in cases of sensitivity to iodides were reported by F Parkes Weber in the *Brit J Dermat* (35 169-180, 1923) Prolonged administration of iodides has caused atrophy of the testicles Mental iodism, like the mental condition due to bromides, has been reported It is interesting that such patients may be free of any eruption due to drugs The eruption in iododerma is commonly seen in the mouth, but not in bromoderma It would be interesting to see how this man reacts to fluorides

DR GEORGE M LEWIS This man holds a responsible position in his firm His story that the mental changes are coincidental with the other changes would indicate that the mental disturbance is intimately connected with the effect of iodides One point I would like to bring up is in connection with the treatment of a patient of this type He has undoubtedly stored a good deal of iodide, and I think that it is dangerous to start immediately with intravenous administration of sodium chloride I contemplate giving small doses of salt by mouth, and perhaps later by vein

Xanthelasmoidea Presented by DR MAURICE J COSTELLO

M C, a boy aged 8 months, is presented from Lenox Hill Hospital with a half-dime-sized, sharply circumscribed, flattened, slightly elevated, smooth, non-hairy, lobulated lesion with xanthelasmic color, which has been present since birth The lesion is nonpruritic, does not change in color on pressure and has not grown unduly in size There are no similar lesions elsewhere on the body

DISCUSSION

DR DAVID BLOOM This eruption is seen not infrequently in infants It appears at birth or soon after and has a tendency to disappear in the first years of life It is a xanthomatous nevus and has therefore been designated by some authors as xanthelasma neviforme (Polano, M K *Arch f Dermat u Syph* 181 139, 1940)

DR WILBERT SACHS Xanthelasmoidea is a form of urticaria pigmentosa Biopsy would tell whether it is urticaria pigmentosa or xanthoma One gets the impression of mycosis fungoides in xanthelasmoidea until the methylene blue stain shows the mast cells

DR FRED WISE I suggest the diagnosis of nevoxanthoendothelioma, which is apparently a nevoid lesion

DR GEORGE C ANDREWS Those lesions are more pinkish than this one Is this not just a juvenile type of xanthoma?

DR FRANK C COMBES I do not know any way to differentiate xanthoma clinically from the nevoxanthoendothelioma of McDonagh Of course, it is unusual to have xanthelasmoidea I think that the only solution is histologic examination They look exactly the same Xanthelasmoidea will eventually flatten down and disappear, whereas the other disease will persist indefinitely

Lupus Erythematosus Presented by DR GEORGE C ANDREWS

A Case for Diagnosis (Verrucae Acuminatae? Infectious Granuloma? Dermatitis Vegetans?) Presented by DR THOMAS N GRAHAM

A Case for Diagnosis (Dermatitis Venenata? Virus Infection?) Presented by DR GEORGE C ANDREWS

Herpes Gestationis Presented by DR JACK WOLF**Lupus Erythematosus Benefited by Suramin Sodium (Naphuride®)** Presented by DR DAVID BLOOM

D K, a woman aged 38, has been treated at the Skin and Cancer Clinic since February 1943 for disseminated chronic, discoid lupus erythematosus involving the face, chest, upper part of the back, upper extremities and scalp. The eruption has been present since 1936.

When first seen in 1943 the patient presented on both cheeks, on the nose and around the mouth erythematous patches covered with thick silvery scales. Both arms, the upper part of the chest and the back showed similar lesions of various sizes. On the scalp there was an erythematous, slightly depressed spot, bald and covered with shiny skin, the size of a silver dollar.

During the past three years the patient has been treated with numerous injections of bismuth compound and liver extract without any appreciable effect on her eruption. Laboratory examinations revealed nothing abnormal except for a leukocyte count which in 1943 was as low as 3,950 per cubic millimeter and which since then has been about 5,000.

Since December 1945, the patient has received intramuscular injections of suramin sodium given in doses of 13 Gm at weekly intervals. After the third injection the patient experienced a temperature of 101 to 103 F, which started five hours after the injection and persisted for about two days, associated with articular pains. The weekly dose was then reduced, first to 0.16 Gm and then gradually raised to the original dose of 0.33 Gm, which the patient then tolerated well. After six injections there was considerable improvement in the eruption, which became much less scaly and less erythematous. She received altogether fourteen injections of suramin sodium, amounting to a total dose of 4.5 Gm. The eruption on the face and in the other areas shows diminution in the size of the plaques, which are much less scaly and less erythematous. The urine and the blood were frequently examined during the administration of the drug and found to be normal.

DISCUSSION

DR DAVID BLOOM: I have observed this patient for the past three years and saw no significant benefit from any kind of treatment. Because of the low leukocyte count I did not attempt gold compound therapy. On the advice of Dr. Rosen I gave the patient small doses of suramin sodium and for the first time in years there was a remarkable improvement in the eruption. Germanin® (German name for suramin sodium) in the dosage given for pemphigus proved to be a dangerous drug, but given once a week in small doses intramuscularly it seems to be safe. It was interesting to read in Jadassohn's textbook (Dermatologie) that germanin® may be administered intramuscularly in a dosage of 0.1 Gm once weekly for a long period. However, it is wise to watch the urine and the blood, as cases of granulocytopenia have been reported from its use.

Secondary Syphilis with Chancre of the Right Nipple Presented by DR NATHAN SOBEL**Oculomotor Nerve Palsy Following Lumbar Puncture** Presented by DR NATHAN SOBEL

J H, a man aged 54, is presented from the Central Social Hygiene Clinic of the New York City Department of Health. He was treated for early syphilis.

in 1917 The treatment was adequate, and since 1926 the Wassermann reaction has remained negative For the past seventeen years the patient has had diabetes, treated with insulin and dietary measures by his physician

The patient was referred by his physician on March 12, 1946, for a spinal tap, which was performed on that day and which was followed by a severe headache which lasted three days On March 21 the patient complained of double vision, which has persisted

Ophthalmologic examination by Dr Charles Becker revealed moderate right blepharoptosis The pupils were slightly unequal, both were round and central and reacted readily to light There was a paralysis of the right internal rectus muscle with diplopia in all fields except when the eyes were directed to the right The right fundus was normal, the left showed extensive showers of cholesterol crystals in the vitreous The diagnosis was paralysis of the third nerve

There was a trace of globulin in the spinal fluid, and red blood cells were present The Wassermann reaction of the spinal fluid was negative, as was the colloidal gold reaction

DISCUSSION

DR JULIUS H POLLOCK (by invitation) About three years ago I had occasion to see a patient with neurosyphilis who after a lumbar puncture had ophthalmoplegia of the right eye About a year ago I saw another patient who had paralysis of the left abducens after lumbar puncture This patient's spinal fluid was normal There is not much in the dermatologic literature either citing such cases or explaining their cause I have spoken to many neurologists, who perform lumbar puncture more frequently than dermatologists do, and it is their impression that paralysis of cranial nerves is seen occasionally after spinal tap or spinal anesthesia, so that its occurrence cannot be regarded as an extreme rarity They further do not believe that the occurrence is related to any particular pathologic condition, inasmuch as it may occur in normal patients as well They had no explanation for the complication

DR NATHAN SOBEL I saw one of the patients Dr Pollock referred to As far as the cause of this phenomenon is concerned, I do not believe that anyone can explain it The prognosis is generally good As a rule, these patients completely recover the motor power of the third nerve

**Yellowing of the Skin, Mucous Membrane Lesions and Nail Changes
Due to Quinacrine Hydrochloride (Atabrine®)** Presented by DR
E W ABRAMOWITZ

A Case for Diagnosis (Bromoderma?) Presented by DR ISADORE ROSEN

E W Abramowitz, M D, *President*

Wilbert Sachs, M D, *Secretary*

May 14, 1946

A Case for Diagnosis (Lichen Planus? Lichenoid Sarcoid?) Presented
by DR MAURICE J COSTFITO

L B, a woman aged 26, was first seen by me in 1943 At that time she had eczema with lichenification involving the labia majora and the perianal regions, which disappeared after one application of low voltage roentgen rays She had, and still has, a bizarre plaque-like eruption which covered the midportion of the

back from the seventh dorsal vertebra to the sacral region. She claimed that this followed a severe contusion and resulting hematoma of the skin which occurred when she fell on her back while roller skating. This eruption is sharply margined, brownish, appreciably depressed beneath the surrounding normal skin and traversed by elongated delicate veins.

She also has irregular reticulated areas of hyperpigmentation and possible atrophy involving the inframammary and left deltoid regions. Recently annular, hyperpigmented scaly somewhat atrophic lesions developed below the lower eyelids and the inner aspect of the left elbow. She has an umbilicated lilac-colored papular lesion on the dorsal aspect of the right wrist. Biopsy specimens were taken from the lesion on the back and the upper outer aspect of the left arm by Dr Klumpp several months ago. Both showed a normal epidermis, no nevus cells and no cellular reaction. Dr Klumpp thought of eruption due to drugs or vitamin C deficiency. The patient has arrested pulmonary tuberculosis.

DISCUSSION

DR FRED WISE This form of eruption was described by Thiebierge and by Tenneson under the name of scleroderma atrophicans. In this patient I believe that there is one lesion of lichen planus on the back of the hand, two different cutaneous diseases are present. A widespread pigmented eruption on the torso is one of the rare manifestations of atrophic scleroderma with hyperpigmentation (Jadassohn, J. Handbuch der Haut- u. Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, p. 731).

DR DAVID BLOOM Such cases, but with less pronounced depression of the lesions, have been presented before this society (*ARCH. DERMAT. & SYPH.* 57:223 [March] 1945). Microscopic examination in one instance showed the features of scleroderma.

DR MAURICE J. COSTELLO The lesion on the back has been present for eighteen years. The lesions in the inframammary and left deltoid regions and on the inner aspect of the thighs have been present for three months. It is interesting to conjecture as to whether the fall she had in childhood had anything to do with the development of the scleroderma on her back. I believe that the discrete annular atrophic lesions on her body are those of lichen planus.

Atopic Eczema Accompanied with Juvenile Cataracts Presented by **DR MAURICE J. COSTELLO**

F. G., a boy aged 18, has had a generalized pruritic eruption for a number of years, accompanied with attacks of asthma which were precipitated by cat hair, dog hair, chicken feathers and ragweed. The eruption is particularly severe on the scalp, face, cubital and popliteal spaces and the hands. The eruption is lichenified, oozing, crusted, hyperpigmented, excoriated and accompanied with edema, redness, and secondary infection of the face and hands. He has a mature cataract of the right eye and a beginning similar lesion of the left eye.

While hospitalized at Bellevue the patient had pneumonia twice, and although extremely ill on these occasions he recovered after large doses of penicillin. He has just returned from a sojourn in Florida. He has shown considerable improvement. He is presented for suggestions as to therapy.

DISCUSSION

DR FRED WISE I have had the best results in cases of this kind with daily intravenous injections of a preparation of calcium gluconate and a bromide salt.

In my experience, it is usually necessary to immobilize the arms of patients to prevent scratching, more especially at night. Padded balsa wood splints are used.

DR SAMUEL M. PECK I would like to detail some of my experiences with the new antispasmodics. I have been disappointed in the use of diphenhydramine hydrochloride (benadryl®) in cases of neurodermatitis. I have obtained amelioration in 1 or 2 cases, perhaps. If these generalized atopic dermatitides are based primarily on a real type of sensitivity and eczematization is secondary, it seems strange to me, unless patients are being treated too late, that relief from itching hasn't been attained with benadryl®. Another drug said to be especially good in these cases is anthallan® (coal tar derivative). My results with this have been equally disappointing. Other observers assure me that the reason my results were not as good as theirs is that one must give 200 to 300 capsules (1 to 1.5 Gm.), even as much as 15 a day, to obtain results. In spite of my having given that amount over a period of months, by and large the results have been disappointing. I have had several patients, especially children, who have taken about 12 to 15 capsules a day and have apparently improved, that is, the recurrences are mild. I know that these patients have periods of exacerbation and improvement, but patients in whom the disease is associated with asthma get along especially well. I have tried the suggestion of Goldman to relieve itching with aminophylline given intravenously. On the wards at Mt. Sinai Hospital there is a patient, a man, who has had a pruritic eruption, most likely a chronic discoid and lichenoid dermatosis type of disease. It is not neurodermatitis. I began to give half the dose, and periods of remission occurred. By giving the amounts Goldman recommends, I obtained just the opposite. Every time I have given this patient full doses, there has been a pronounced exacerbation of itching. On the wards of the hospital the interns have been trying intravenous injections of procaine hydrochloride, and I have been surprised at the results, which are certainly better than with calcium bromide. I have tried calcium bromide and gluconate with good results in some instances.

DR MAURICE J. COSTELLO I have tried benadryl®, anthallan® and tripeleminamine hydrochloride (pyribenzamine®). Anthallan® has been of no value in my experience. Benadryl® may cause drowsiness, and I know of 2 patients who had fainting spells following its administration. One had convulsive movements after taking ½ capsule (25 mg.) and this was repeated after a smaller dose. Most patients will complain of some dizziness and many complain of drowsiness. Juvenile cataracts occurring in association with atopic eczema, I believe, are due to the trauma of rubbing the eyes to relieve itching. I saw this boy stroking his eye forcibly to relieve pain, and I examined him expecting to find a cataract.

Mycosis Fungoides with Histologic Picture of Reticulum Cell Sarcoma
Presented by DR. FRED WISE

A Case for Diagnosis (Leprosy? Sarcoid?) Presented by DR. MAX SCHEER

Necrobiosis Lipoidica Diabeticorum Presented by DR. GEORGE M. LEWIS

A Case for Diagnosis (Poikiloderma? Generalized Dermatitis Atrophicans?) Presented by DR. E. W. ABRAWOWITZ

P. C., a man aged 61, came to the Skin and Cancer Clinic complaining of a generalized eruption of twenty years' duration. The entire skin is involved, showing erythema, with branny scaling which is most pronounced on the abdomen,

thighs and buttocks. A positive Nikolsky sign was obtained on the back when the patient was first seen. The elbows, buttocks and thighs show, also, wrinkling which strongly suggests atrophy of the skin. The face and the extensor surface of the forearms show hyperpigmentation in addition. The glands are not enlarged. The biopsy diagnosis was poikiloderma. The past and family histories were noncontributory. The Wassermann reaction of the blood was negative. The results of blood cell and differential counts have not been reported yet.

DISCUSSION

DR FRED WISE. My impression is different than that of the pathologist. This patient has a universal atrophy of the skin which is wrinkled, with the blood vessels shining through. Cases of this kind were described in 1910 by Finger and Oppenheim with the diagnosis of dermatitis atrophicans progressiva. I know of no type of mycosis fungoides preceded by atrophy. In this case, poikiloderma as well as infiltration is absent.

DR. DAVID BLOOM. Cases of poikiloderma are reported which have lasted ten or twenty years, and then manifestations of mycosis fungoides developed. This patient shows in some areas, such as the gluteal regions, the posterior aspect of the thighs and the elbows, the clinical appearance of poikiloderma, which justifies the consideration of this diagnosis in the patient.

DR E. W. ABRAWOWITZ. When this patient was first observed, there was considerable redness and scaling of the entire body, including the face. The skin loosened easily on rubbing (Nikolsky's sign). The eruption, if viewed from the location on the lower extremities, was typical of acrodermatitis chronica atrophicans. It was, however, too generalized, and some form of atrophoderma was considered. Jacobi's poikiloderma is a possibility, but in my opinion this is not the final diagnosis.

Contact Dermatitis (Rubber Gloves?) Presented by DR GEORGE M. LEWIS

A G., a 40 year old Negro housewife, is presented from the New York Hospital because of a peculiar hyperkeratotic folliculopapular eruption limited to the right wrist and adjacent surface of the forearm. She had been bothered with chronic eczema of the hands for the past year, while for several months prior to the onset of the present trouble and up to the present time a rubber glove has been worn on the right hand. The present illness began one month ago as a few areas of follicular accentuation but has steadily grown worse. The patient has incidental, well treated, late latent syphilis. Circling the right wrist and lower part of the forearm is a closely set folliculopapular eruption, the individual lesions of which are hard brownish conical papules, surmounted frequently by discrete hyperkeratotic spines. Some of these follicular plugs can be removed by pressure.

DISCUSSION

DR SAMUEL M. PECK. Contact dermatitis from rubber gloves occurred in almost epidemic proportions about eight months ago before one manufacturer withdrew his product from the market. The gloves contained either an anti-oxidant or an accelerator which was the causative agent. The follicular type of dermatitis which this patient presents comes in my experience only from contact with the petroleum hydrocarbons and tar. Even then, with follicular hyperkeratotic papules, there is definite hyperpigmentation. I was able to tell from histologic examination what the occupational cause was, whether petroleum hydrocarbons,

tar products or the like I do not know of any other chemical outside of that group which will produce this dermatitis. Certain waxes will do it, but I do not know whether ordinary petrolatum as sold in the pharmacy can cause it, so that I do not see how a diagnosis of ordinary contact dermatitis can be made here. It is an unusual reaction.

DR FRED WISE May I ask whether rubber gloves might contain a tar product?

DR SAMUEL M. PECK I doubt it. I do not know of any.

DR DAVID BLOOM Does not the fact that the involvement is of the lower part of the forearm rather than the hand speak against contact dermatitis from the rubber glove?

DR JACK WOLF In defense of Dr. Lewis' diagnosis is the sharp limitation at the upper part of the glove, and also the fact that there are definitely hyperkeratotic lesions instead of the comedo and pustule which results from contact with hydrocarbons and tars. The eruption may not be one of hypersensitivity but is nevertheless suggestive of contact dermatitis.

DR ANTHONY C. CIPOLLARO I do not believe that dermatitis of the wrist and lower portion of the forearm from a rubber glove without a dermatitis of the hands is unknown. I have had several such cases, and observed 1 in my office only yesterday. If this eruption is not caused by rubber gloves, I do not know what else would have produced it.

DR GEORGE M. LEWIS I saw the patient for the first time this afternoon, and, while I questioned her carefully, I was unable to get any leads regarding the cause, except rubber gloves. I will make tests and also a biopsy.

Lichen Pilaris Seu Spinulosus Presented by DR JACK WOLF

Dermatitis Herpetiformis, Dermatitis Medicamentosa and Neuritis (Arsenic) Presented by DR GEORGE M. LEWIS

A Case for Diagnosis (Lichen Planus? Secondary Syphilis?) Presented by DR GEORGE M. LEWIS

Nevus Unius Lateris with a Microscopic Picture of Psoriasis Presented by DR GEORGE M. LEWIS

Psoriasis Guttata (Secondary Psoriasiform Syphilis?) Presented by DR MAURICE J. COSTELLO

Iododerma, Iodism Presented by DR GEORGE M. LEWIS

E. A., a man aged 52, was previously presented before this society on April 9, 1946. He had taken strong iodine solution for six years after a thyroidectomy. Cutaneous lesions first appeared in February, with gradual progression. After his presentation at the last meeting, the patient was given salt by mouth beginning with 15 grains (97 mg) daily and increasing to 30 grains (194 mg) daily. After one week he was given an intravenous infusion of 500 cc of isotonic sodium chloride solution, and this was repeated on three subsequent days. About two hours following the last infusion there developed shaking chills and a temperature of 102 F, accompanied with headache which gradually increased in severity. There were some nausea and general malaise. Examination showed that the old

erythema multiforme-like lesions were the sites of multiple hemorrhages, and there were, in addition, many other purpuric lesions in previously uninvolved areas on the body. The oral mucosa was normal. The patient was hospitalized, and the white blood cells were found to number 2,400, a transfusion of 500 cc of whole blood was administered. Following the transfusion there was temporary improvement, but the following day the headache again became severe, the patient was drowsy and slightly confused, the temperature remained elevated and his cutaneous lesions had become more inflamed. Because of the possible encephalopathy, 500 cc of dextrose solution (10 per cent) was administered intravenously and repeated on two successive days. The systemic symptoms then rapidly disappeared, and the tendency to hemorrhagic lesions diminished. After an interval of several days, salt therapy was cautiously resumed (5 grains [32 mg] three times daily). There was an immediate exacerbation of the eruption with new purpuric lesions, accompanied with headache and a drop in leukocytes. During this month of observation there has been a consistent mild rise of temperature in the afternoon.

The appearance has altered considerably from the April presentation in that there are no target lesions now present and the contact dermatitis of the face has subsided. There are still fresh hemorrhagic lesions of the legs. Disseminated over the body are small plaquelike lesions, many of which show scaling, with a fine diffuse involvement of the face and neck.

DISCUSSION

DR ISADORE ROSEN: I believe that the use of salt intravenously in cases in which iodides are responsible for the eruption should be approached with caution because of the severe reactions which follow such administration. This case illustrates the fact. I have had a similar experience in which this type of therapy was carried out in a patient with an eruption due to iodides.

DR FRED WISE: Do I understand correctly that the patient received 5 grains (32 mg) of sodium chloride and that amount caused an exacerbation? The man gets 5 grains of salt with a single meal. I do not see how it could cause an exacerbation unless iodized salt was used.

DR HERMAN SHARLIT: He would get 8 to 10 Gm of salt a day in food. I do not know whether 0.5 Gm or 0.3 Gm could cause such an exacerbation.

DR MIHRAN B. PAROUNAGIAN: This is more than iododerma. I think that it is generalized lupus erythematosus, and I do not believe that the administration of salt had anything to do with it.

DR MAURICE J. COSTELLO: The eruption and its distribution are suggestive of acute lupus erythematosus, as is also the leukopenia. I think that the erythrocyte sedimentation rates should be determined and that the patient should be given crude liver extract, 3 cc three times a week.

DR FRANK CORMIA (by invitation): The erythrocyte sedimentation rate was normal.

DR MAURICE J. COSTELLO: I believe that that would rule out lupus erythematosus.

DR SAMUEL M. PECK: All speculations as to why the ingestion of a small amount of salt could produce a given result do not detract from the observations Dr Lewis has made. He gave salt tablets and an exacerbation occurred. One might argue that the cause could be in the enteric coating and ask Dr Lewis to make the test with ordinary table salt. When a certain procedure has been

carried out and the results are recorded by a good observer, these observations cannot be disregarded. The reasons for them are something else.

DR FRED WISE I understand from reading the articles of Montgomery of the Mayo Clinic that the diagnosis of acute lupus erythematosus is not always readily confirmed by microscopic examination, so that it is possible that this is acute lupus erythematosus in which the histologic change is not characteristic or has not had time to develop.

DR E W ABRAMOWITZ I agreed with the diagnosis of iodism because the patient had an enlargement of the parotid glands, was mentally disturbed, had some fever and had been taking iodides. The eruption was of the erythema iris type and purpuric. My co-workers and I had a patient at the Skin and Cancer Unit who received iodides for hyperthyroidism and who had an eruption believed at first to be due to the iodides. On further observation this eruption turned out to be disseminated lupus erythematosus. One fact remains to be explained, and that is why 5 grains of sodium chloride caused an aggravation of the eruption and particularly purpura. It is possible for an intravenous injection to cause a release of iodides into the circulation. Deaths have been attributed to the administration of isotonic sodium chloride solution to patients with mental bromism or iodism in whom dangerously large amounts of these elements were already present in the body fluids. Although it is unusual to see disseminated lupus erythematosus in a man of this patient's age, the possibility must be entertained at present. I never heard of lupus erythematosus activated by sodium chloride.

DR MAURICE J COSTELLO Strong iodine solution has been advised in the treatment of acute lupus erythematosus. If this patient has that disease, it is odd that it should be precipitated by the administration of that particular drug.

DR FRANK CORMIA (by invitation) The reaction to the patch test with 25 and 50 per cent potassium iodide was negative.

DR GEORGE M LEWIS At the last meeting of this society there was unanimous agreement that this patient had an eruption due to iodides. We start, then, with the premise that this man had a proved eruption due to iodides and iodism. It would seem logical to assume that allergy might be invoked to explain both the cutaneous and the cerebral symptoms. I have entertained a diagnosis of lupus erythematosus, but have nothing to substantiate that impression. The white blood cell count has fluctuated so much that the leukopenia which was present at times may probably be disregarded. The erythrocyte sedimentation rate was normal, the kidneys were apparently free of disease, and results of tests of hepatic function were normal. At this time I still favor the diagnosis of iododerma and iodism.

David Bloom, M D, President

Wilbert Sachs, M D, Secretary

Oct 8, 1946

A Case for Diagnosis (Acrodermatitis Chronica Atrophicans? Majocchi's Disease? Telangiectasia?) Presented by DR E WILLIAM ABRAMOWITZ

Sycosis Vulgaris Blepharitis Presented by DR ANTHONY C CIPOLLARO

M L, a man aged 45, was first seen by me on Aug 14, 1946. Seven years ago a rash developed on the upper lip, which gradually spread to the chin and the eyelids. The eruption became so severe that it caused ectropion of both lower eyelids. The patient had been treated with topical remedies unsuccessfully.

The patient has lesions typical of sycosis vulgaris affecting the upper lip and the chin. The eyelids are everted. There is constant lacrimation. The lashes on the lower lids are absent, causing deformity. The ectropion, of course, is part of the picture of the sycosis vulgaris.

The patient was treated with compresses of hot boric acid solution during the daytime, and at bedtime he applied 3 per cent ammoniated mercury ointment. He was given *Staphylococcus* toxoid injections at weekly intervals and low voltage (70 kilovolts) unfiltered roentgen therapy, in doses of 75 r each week. Up to September 26 he received a total of seven treatments, with substantial improvement in the condition.

DISCUSSION

DR THOMAS N GRAHAM: Since the eye can stand as much roentgen radiation as the skin, there is no danger in treating the eyelids. This has been proved by Jones and Alden (*Roentgen Ray Treatment of the Eye*, ARCH DERMAT & SYPH 43 92-98 [Jan] 1941). I have seen a number of patients from the New York Eye and Ear Infirmary treated for conditions of the eye such as corneal ulcer, with the dosage as high as that used on the skin—as many as twelve exposures of 75 r each. No damage resulted to the eyelids or to the eyes.

DR JACK WOLF: Dr Cipollaro has obtained a good result in this case. I do not know how many of us have used roentgen rays in the treatment of dermatitis of the eyelids. I know that during the years I was associated with Dr Wise we used roentgen rays on eyelids and were not particularly afraid, and we had no bad results. I think that this patient would now probably profit from treatment with brilliant green.

DR GEORGE M LEWIS: Since the cilia are epilated by the disease, there may be regrowth of hair, and, if so, it will be interesting to see whether there is a recurrence. However, the result at this time is good, and Dr Cipollaro is to be congratulated.

DR HERMAN SHARLIT: The result is excellent. I would like to know how much credit Dr Cipollaro gives to the roentgen treatment and how much to the topical remedies he used, each of which might be effective. I know nothing about the possibility of harm resulting from exposing the eyeball to roentgen rays directly, but I never do it. I do not want to take the responsibility, even though it may be safe.

DR E W ABRAMOWITZ: Dr Cipollaro has been fortunate to obtain an excellent result in a type of case which gives so much trouble. Ammoniated mercury is still one of the most effective remedies for sycosis in my experience. Barring sensitivity to mercury, these patients usually show improvement. Another important point here is that improvement in the eruption was coincidental with the stopping of the nasal discharge. I have questioned patients who had had atopic dermatitis for many years and then had cataracts and found that some of them had never undergone roentgen therapy. I certainly think that it is safer not to expose the eye if it is not necessary, but, if it is necessary, it is good to know that there are some patients who can take a certain amount of roentgen rays to the eyes. Sycosis sometimes disappears irrespective of the methods used, but relapses are common.

DR MAURICE J COSTELLO: I think that the eye can tolerate a certain number of fractional doses of roentgen rays, but I am certain of the fact that large doses administered in the treatment of epitheliomas will produce changes in the eye, especially cataracts. Cataracts occur much more frequently in atopic dermatitis.

than is generally known I make it my rule to have an ophthalmologist examine these patients soon after their first visit to my office to rule out cataract formation. The occurrence of cataracts, even though not large enough to interfere with vision, is higher than one would suspect, cataracts which have been present before roentgen rays were administered. I inform the physician who referred the patient, but do not tell the patient because it may be years before the cataract interferes with vision.

DR. GEORGE C. ANDREWS: Cataract can occur spontaneously in conjunction with hemangioma of the lid. I presented a patient with a hemangioma of the eyelid accompanied with cataract. She had never received any roentgen or radium treatment (Hemangiomas of Orbit with Cataract, *ARCH. DERMAT. & SYPH.* 53:206 [Feb.] 1946). It is an important case to put on record because of the tendency to ascribe cataracts to irradiation.

DR. ANTHONY C. CIPOLLARO: I decided to treat the eyelids with roentgen rays without using protective eye shields because there is insufficient scientific evidence that the quality and quantity of radiation administered by dermatologists for such conditions are harmful. In fact, the article by Jones and Alden proves the reverse to be true. These authors showed that the eyeball tolerates as much as if not more roentgen rays than the skin. Therefore, one should not expect any danger to the eyeball if the amount of roentgen rays administered is insufficient to produce permanent cutaneous changes. Roentgen rays and grenz rays are used at several clinics for the treatment of various diseases of the eye and eyelids. There have been no reports of damage to the eyeball or eyelids from the use of moderate doses of low voltage unfiltered roentgen rays. From the available evidence, I think that it is safe for dermatologists to employ limited quantities of roentgen rays in small doses for the treatment of lesions of the eyelids.

Chronic Benign Familial Pemphigus (Hailey-Hailey) of the Axillas, Neck and Scalp Presented by DR. MAX SCHEER

Rhinophyma. Presented by DR. ANTHONY C. CIPOLLARO

J. C., a man aged 65, was first seen by me Aug. 14, 1946. Seven years ago the nose became red and a pendulous mass began to form, which steadily grew to the size of a baby's fist. He has been embarrassed by the growth but has done nothing about it.

Examination showed a tumor about the size of a baby's fist hanging from the nose. The tumor was soft and appeared to be made up entirely of sebaceous glands. Because the tumor hung in front of the mouth, it interfered with talking and eating. The remainder of the nose showed definite manifestations of rhinophyma.

On September 10, with procaine anesthesia, the lesion was removed with the cutting current. Several large vessels had to be ligated with fine surgical gut, with purse-string sutures. The entire surface of the lesion was then coagulated. There was only slight oozing during the first two weeks of the healing process.

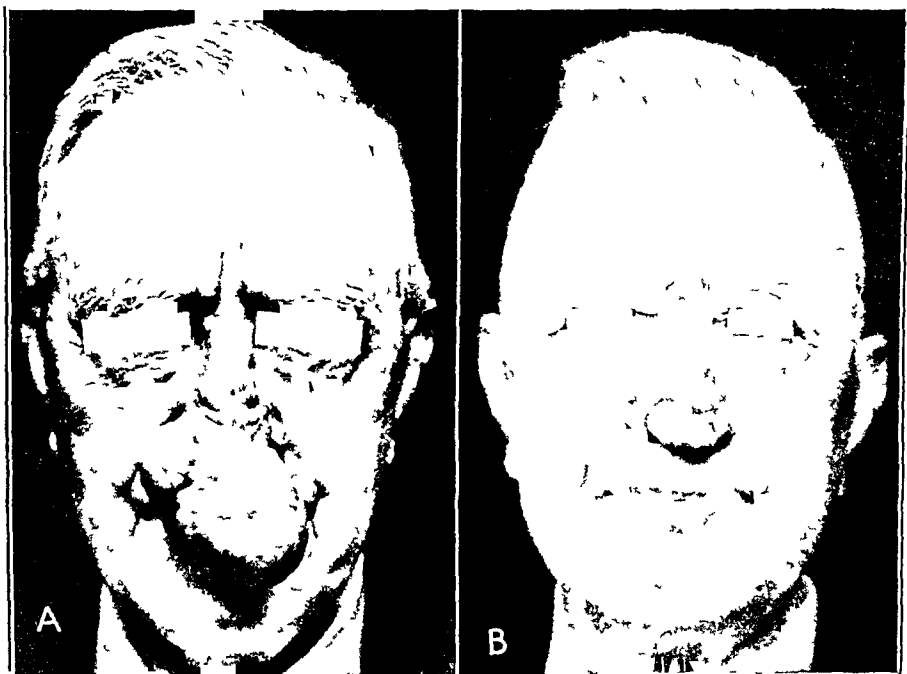
Parapsoriasis en Plaques Associated with Mycosis Fungoides Presented by DR. ISADORE ROSEN

Tinea Corporis Presented by DR. JACK WOLF

M. K., a man aged 63, is presented from the Skin and Cancer Unit with a widespread eruption of approximately one year's duration. During this period he has been treated with various remedies by several physicians, without improve-

ment The eruption has continued to spread until it now covers almost the entire body

The patient presents a profuse, small papular eruption bordered by numerous arciform, erythematous, gyrate and elevated strands of smaller and larger size on the torso and extremities The lesions also extend onto the head and neck The palms are dry, thickened and mildly scaly All the finger nails of the left hand are a dull white, lack luster and at the free margins present a considerable amount of subungual hyperkeratosis The nails of the right hand are unaffected The unilateral involvement of the nails is of considerable significance in the case since the patient is a bootblack and frequently his left hand is in the shoe while he brushes with his right hand



Rhinophyma *A*, before treatment, *B*, after treatment with the cutting current

Direct examination of the scales showed many mycelia on culture, *Trichophyton purpureum* was identified The trichophytin test gave no immediate reaction Histologic examination of a piece of tissue from one of the arciform lesions showed only superficial dermatitis (Dr Charles Sims)

DISCUSSION

DR GEORGE M LEWIS These cases of widespread disease sometimes respond well to therapy The more resistant infections are those which involve the hands, feet and nails Sometimes the milder remedies are better in this type of disease, and I would suggest a trial of 3 per cent salicylic acid in 70 per cent alcohol

DR WILBERT SACHS An interesting point to me was the well defined sharp border of normal skin within some of the lesions One sees this at times in psoriasis and in mycosis fungoides I do not offer either of these as a diagnosis in this case

DR HERMAN SHARLIT I believe that the free areas are not immune and that the organism will grow into them

DR E WILLIAM ABRAMOWITZ I have seen cases of less extensive disease disappear with treatment with benzoic and salicylic acid ointment Of course, the hands and nails, as Dr Lewis mentioned, would be a problem

DR JACK WOLF This is as extensive an eruption of T purpureum infection as I have seen I have had some excellent results with as mild a remedy as boric acid ointment, and some respond well to desenex[®] ointment (contains undecylenic acid and zinc undecylenate in an ointment base) Unfortunately, the eruptions usually recur

A Case for Diagnosis (Lichen Planus Atrophicus? Kaposi's Sarcoma?)
Presented by DR MAX SCHEER

Raynaud's Disease Presented by DR NATHAN SOBEL

Papulonecrotic Tuberculid of the Lower Extremities (Sarcoid?) Presented by DR FRED WISE

Favus Presented by DR FRED WISE

C R, an Italian girl aged 18, born in this country, registered at the Skin and Cancer Unit on Sept 17, 1946, presenting lesions of thirteen years' duration There is no history of a similar infection in her parents, brother or 2 sisters At 8 years of age she was told at the Brooklyn Hospital to have her hair cut off, which she refused No medicine was prescribed The second time she consulted a physician was six months ago, he told her that it was a fungous growth and prescribed a salve The patient applied the salve for several weeks, and the crusts were thereby removed, leaving a raw surface There is occasional itching

When first seen there were yellowish crusted patches with pea-sized to large shallow depressions The lesions are located on the anterior and right lateral half of the scalp, extending 1 inch (2.5 cm) from the hair margin of the middle of the forehead to the middle of the scalp, downward for an area of 7 inches (17.5 cm) and ending 1.5 inches (3.75 cm) above the lobe of the right ear On October 2 the lesions were erythematous with irregular small cuplike depressions which appeared atrophic, covered only with fine crusting, denuded of most of the hairs, the remaining hairs being matted together

Since September 17 the patient has been using a salve containing 2 per cent salicylic acid and 5 per cent ammoniated mercury The Wassermann and Kahn reactions of the blood were negative The hemogram revealed hypochromic anemia with a red blood cell count of 4,820,000 and 12.2 Gm of hemoglobin (76 per cent) Direct examination showed spores and mycelia Examination with the Wood filtered light showed a greenish fluorescence of the hairs The culture showed the characteristics of *Achorion schoenleini*, the colonies being waxy looking with many folds

DISCUSSION

DR NATHAN SOBEL I am interested in knowing why the infection should stay limited for so many years to one area

DR E WILLIAM ABRAMOWITZ I have seen only one or two domestic cases besides this one, and all of them were contracted in early childhood Dr Lewis will probably recall the last patient There was involvement of the scalp and finger nails She had been treated by epilation several times, but each time there was a recurrence because she reinfected herself from the finger nails

DR GEORGE M LEWIS The question uppermost at this time would seem to be, should roentgen rays be given? Dr Cipollaro can perhaps give more data on the dangers involved at this age. Before roentgen rays are given—if this is decided on—I think that the scalp should be vigorously treated with shampoos and fungicides so that the infection on the surface of the scalp is controlled. Recurrences may take place because of faulty treatment beforehand and lack of treatment after roentgen rays have been administered. There must be good preliminary therapy and good after care if one hopes to obtain a cure with roentgen rays in these patients.

DR ANTHONY C CIPOLLARO Dr Lewis has brought out the important points of discussion in this case. I have not treated many patients with favus with roentgen rays, but in those I have treated, my general impression is that the results have been poor.

DR DAVID BLOOM In a case of favus in a doctor's wife which I treated by epilation, the result was good. Many years ago I gave treatment in about 60 cases of tinea capitis in children with thallium. There were few toxic reactions, as the treatment was limited to young children. The older the child and the more it weighs, the greater the danger of toxic reactions.

DR FRED WISE I will bear in mind the suggestions made by Dr Lewis and Dr Cipollaro. I wonder whether it is necessary to remove all the hair. Should one cut it all off?

DR GEORGE M LEWIS I have had a few good results with partial epilation, but it has to be done carefully and one has to observe a rigid technic.

DR ANTHONY C CIPOLLARO It is worth while to treat only one area. If after all these years the infection has remained localized to one area, it seems unnecessary to epilate the whole head.

Tinea Capitis in a 13 Year Old Girl Presented by DR ANTHONY C CIPOLLARO

David Bloom, M D, President

Wilbert Sachs, M D, Secretary

Jan 14, 1947

Xanthoma Juvenilis Presented by DR NATHAN SOBEL

J M M, a white boy aged 4 months, has on the bridge of the nose near its base a large pea-sized, moderately elevated, flat, smooth, yellowish white node which has been present since birth.

DISCUSSION

DR JACK WOLF The lesion looks clinically like xanthoma, but on account of its soft and seemingly cystic character it might be punctured to see if fluid is present.

DR MAURICE J COSTELLO The possibility of an embryonal inclusion cyst should be considered. This is a common location for such a lesion. This one is fairly soft, and the color is that transmitted by sebaceous material rather than xanthoma.

DR MAX SCHEER The lesion impressed me also as being possibly a sebaceous cyst. I think it should be explored with a needle.

DR WILBERT SACHS I agree with the diagnosis of sebaceous nevus I have seen a case in which the entire nose was involved This lesion will probably break down and discharge sebaceous material

DR DAVID BLOOM In spite of the fact that the lesion is softer than usual, I favor the diagnosis of nevoxanthoma I think there would be no harm in puncturing the lesion

DR NATHAN SOBEL The lesion has been enlarging since I first saw it two months ago I will keep it under observation

A Case for Diagnosis (Behcet's Syndrome?) Presented by DR HERMAN SHARLIT

V K, a woman aged 28, has been under my care since September 1946 She has had sores in the mouth for twenty-two years, occasionally associated with vaginal ulcers During my period of observation I have seen ulcerations on the pharynx, tonsils, buccal mucosa, tongue and lips The patient has received many forms of treatment and reports that the local application of arsphenamine in glucose has hastened healing I have administered vitamins, bismuth and the antihistaminic drugs, to no avail

DISCUSSION

DR JACK WOLF I know of no other diagnosis that can be entertained If the patient has not been vaccinated repeatedly, this procedure might be tried

DR MAURICE J COSTELLO I agree with Dr Graham that it is periadenitis mucosa necrotisans recurrens It is not my conception of Behcet's syndrome as I have seen it That disease is much more extensive, with destruction of the areas affected accompanied with ocular involvement This young woman has had a number of lesions with no evidence of scarring, and all the lesions disappeared during her pregnancy

DR GEORGE M LEWIS If antimony potassium tartrate has not been given, I would suggest a course of that drug

DR WILBERT SACHS I agree with the diagnosis of Behcet's syndrome, even though the ocular signs are missing Cases have been described without these findings In a patient whom I showed recovery took place after pneumonia with high fever Therefore, fever therapy might prove helpful

DR FRED WISE Although the buccal lesions might be one of the symptoms of Behcet's syndrome, I would hesitate to accept such a diagnosis in the absence of associated lesions and constitutional disturbances I suggest the diagnosis of periadenitis mucosa recurrens and would give smallpox vaccine a therapeutic trial

DR HERMAN SHARLIT This patient had vaginal lesions also but never had ocular lesions We have tried all modes of therapy suggested tonight The lesions disappeared during pregnancy It seems to be on occasions when the general metabolism is much upset that these patients get well temporarily

Balanitis Xerotica Obliterans Presented by DR NATHAN SOBEL

R P, a man aged 58, has had a penile infection of twenty years' duration The entire glans and a rim $\frac{1}{4}$ inch (0.64 cm) wide on the adjacent mucous portion of the prepuce are thin, bluish and atrophic, with some brownish pigmentation in a few small areas The urethral orifice has shrunk to about half its original size At present there is no obstruction to the urinary stream The trauma of intercourse frequently results in tiny abrasions Except for soothing emollients, the patient has had no treatment.

Multiple Telangiectases (Hereditary Telangiectasia of Rendu-Osler-Weber?) Presented by DR NATHAN SOBEL

C H, a white girl aged 5, is presented from the Skin and Cancer Unit, where she was first seen on Jan 13, 1947, with an eruption which has been present since the age of 15 months. It appears first on her face and gradually spread to other areas. She has never had any hemorrhages. One aunt gives a history of nosebleeds, cause unknown.

On the face and hands are numerous small areas of telangiectasia. These are also present on the vermillion border of the lips. On the right buccal mucosa there are a few pinhead-sized, red areas. Over the whole body, but especially noticeable on the legs, there are numerous large pea-sized, blanched, flat spots, in many of which is a central dilated blood vessel without any radiating branches. On the body and arms there are port wine marks of various sizes.

DISCUSSION

DR MAURICE J COSTELLO: I think the lesions on the legs are punctate telangiectasis with avascular areas around them.

DR DAVID BLOOM: The remarkable feature is the numerous, round, depigmented lesions on the extremities which have a small red or brown punctum in the center resembling leukoderma centrifugum.

DR WILBERT SACHS: My contention is that it was capillary and not arterial, or the lesions would not bleed as easily.

DR NATHAN SOBEL: I felt that the central puncta were dilated blood vessels, consequently, I do not believe they were "halo" nevi. As far as telangiectasia due to syphilis is concerned, a serologic examination is indicated. I have also seen 1 patient with telangiectasis on the palm in late acquired syphilis.

Pachyonychia Congenita with Keratoderma of Palms and Soles and Leukoplakia Oris Presented by DR FRED WISE

S H, a woman aged 40, registered at the Skin and Cancer Unit on Jan 23, 1947, presenting various cutaneous lesions. She has a son aged 16 who has similar lesions and who is being presented simultaneously. A daughter aged 19 is said to be normal, and there is no history of a similar disturbance in other members of the immediate family or in distant relatives. From the age of 1 year until she was 7, the patient every year had "skin sores" all over the body, these became blistered and later scabby and crusty. They would last all summer, so that she was obliged to stay in the hospital. At the age of 22 she had an infection of the mouth, and 25 teeth were extracted at one time. Her hands and feet are always cold. Menstruation has been regular. She has been having migraine headaches since the age of 24. Her general health has been good except for difficulty in walking because of the callouses. She is intelligent and alert.

A week or two after birth the nails of the fingers and toes became discolored and thickened, reaching their height within a month or two. They have changed little since that time. A slight injury causes an infection, and the entire nail is cast off. The lesions on the feet first appeared at the age of 18 months, when she began to walk, and became more pronounced and progressively thicker as she grew older, so that at times her mother was obliged to pare them off. They are painful on walking. In 1933 a skin graft was performed on the left heel, with poor results. She has a continuous tired feeling.

At the points of pressure on the soles, heels and toes, symmetrically distributed, are hard, thick, painful, hyperkeratotic, lemon-colored growths, tender to touch. On the right palm at the base of the metacarpals and the interphalangeal joints are similar growths. All the toe nails are dry, dystrophic and blackish in color, with irregular, rough surfaces. The finger nails are long, thickened, curved, discolored and tapering off toward the end, with the nail of the left ring finger partially broken off. On the right buccal mucosa are small, match head-sized, leukoplakic patches. The entire dorsum of the tongue is covered with whitish, adherent patches and with leukoplakic areas which are particularly noticeable on the sides. The scalp is covered with dry, scaly, diffuse, seborrheic patches. There are two hairy, pea-sized, pigmented moles on the chin. The hands and feet are cool to touch. The integument is dry.

The Mazzini reaction was negative. The urine was normal. The hemogram revealed a normocytic anemia, with 3,710,000 erythrocytes, a hemoglobin content of 12.2 Gm per hundred cubic millimeters (73 per cent). The color index was .98. The leukocyte count showed 8,000 cells per cubic millimeter, with 50 polymorphonuclear neutrophils, 41 lymphocytes and 5 monocytes.

An ophthalmologic examination including the eyegrounds and a slit lamp examination of the cornea revealed nothing abnormal.

The total carotinoid content of the blood was 170 units per hundred cubic centimeters (normal, 50 to 100). The vitamin A content was normal.

Vitamin A, 75,000 units daily for a period of six weeks, was taken until three weeks ago. Since February 19 the patient was advised to continue taking 50,000 units of vitamin A and 10 mg of vitamin E three times a day and $\frac{1}{4}$ grain (0.015 Gm) of thyroid extract. Salicylic acid salve, 20 per cent, was prescribed, to be applied to the callouses three times a day.

Pachyonychia Congenita with Keratoderma of Palms and Soles and Leukoplakia Oris. Presented by DR FRED WISE

Lupus Miliaris Disseminatus Faciei. Presented by DR JACK WOLF

Dermatitis Venenata of the Feet and Popliteal Areas (Nylon). Presented by DR JACK WOLF

A Case for Diagnosis (Angioma Serpiginosum?) Presented by DR FRED WISE.

M. L., a woman aged 38, registered at the Skin and Cancer Unit on Nov 21, 1946, complaining of lesions of about fifteen years' duration. Her first and only pregnancy resulted in a stillbirth in October 1945. The Rh factor of both the patient's and her husband's blood was normal. The basal metabolic rate in April 1946 was said to be on the "low side," and she took thyroid extract tablets for two months. She gives no history of previous cutaneous disorders.

The eruption first came out on the chest. During pregnancy it began to appear on the neck and has been "creeping up and down." The eruption is worse during the warm weather.

There is a well defined, fairly symmetric, rose red eruption on the sides of the neck, lower third of the face and front of the chest. It is most pronounced on the right side, where it involves two thirds of the right clavicle, arranged in a V shape. The lesions consist of pinpoint to pinhead to match head-sized spots and irregular, diffuse patches. Most of the spots are light brownish, while the patches are rose red. The lesions on the neck consist mostly of isolated pinpoint

to pinhead-sized spots which are discrete and grouped in linear formation. Most of the lesions on the front of the chest and clavicle fade on pressure, revealing yellowish spots and small telangiectatic capillaries. The spots on the neck show little change on diascopic pressure. The patient has mild premature alopecia and seborrhea of the scalp.

The Mazzini reaction was negative and the urine normal. Mild hypochromic anemia was present. The blood and the ascorbic acid content were normal. The basal metabolic rate was — 11 per cent.

After biopsy of a lesion from the left retroauricular region the condition was diagnosed by Dr Charles F. Sims as "superficial dermatitis." The epidermis showed no noteworthy changes. The vessels of the upper part of the corium were moderately dilated and their walls surrounded by a sparse cellular reaction composed of small round cells, wandering connective tissue cells and polymorphonuclear leukocytes. Around the vessels was a parenchymatous edema of the supporting framework.

DISCUSSION

DR NATHAN SOBEL: All I can call it is multiple telangiectasis.

DR SAMUEL M. PECK: Dr Klemperer at Mt Sinai Hospital is attempting to study these changes pathologically. He tells me that they are going to study the phosphatase in the vessel walls.

DR MAURICE J. COSTELLO: I think there is no doubt that light has something to do with these telangiectases. The submental area which is not exposed to sunlight is free.

DR HERMAN SHARLIT: These are common observations. Many persons get dilated blood vessels in areas exposed to sun. This patient also has a persistent erythema of the chest, which is not normal. I believe the condition is due to an unusual response to sun.

DR FRED WISE: I was thinking, when Dr Peck spoke of enzymes, that there must be some relationship to exposure to wind or cold, because if the eruption were due to some peculiar chemical changes due to enzymes, we would expect to see it on some other part of the body. Possibly only the parts exposed to wind and weather are affected.

David Bloom, M D, *Chairman*

Wilbert Sachs, M D, *Secretary*

Feb 11, 1947

Sarcoidosis Presented by DR ISIDORE ROSEN

G B., a Negro woman aged 57, registered at the Skin and Cancer Clinic in February 1947, complaining of an eruption on the face of one year's duration.

On the face there are numerous pinhead-sized to pea-sized, firm, raised nodules, less dark than the rest of the skin. The tumors are aggregated and in some areas confluent, involving particularly the inner canthi of the eyes, the nose and adjacent parts of the cheeks, upper lip and chin.

The serologic reaction of the blood was negative for syphilis. The blood cell count showed hemoglobin 60 per cent and leukocytes 4,000, with 57 per cent lymphocytes, 40 per cent polymorphonuclear leukocytes, 9 per cent monocytes and 4 per cent eosinophils. A roentgenogram of the lungs showed large masses of a lymphomatous type protruding from the hilus into both central lung fields. The peripheral fields were clear except for a slight degree of secondary root gland

thickening The reaction to the tuberculin test was negative in a dilution of 1 10,000 Biopsy confirmed the diagnosis of sarcoid

DISCUSSION

DR FRED WISE On the basis of the histologic description, the diagnosis of sarcoid appears to be acceptable, although the eruption resembles disseminated miliary tuberculosis The soft, pedunculated tumors of the upper eyelids appear to speak against the diagnosis of Boeck's sarcoid

DR WILBERT SACHS I believe that I made a clinical diagnosis of disseminated miliary lupoid, and this is the same as disseminated miliary sarcoid

DR SAMUEL M PECK If the patient were not a Negro, I would not think of sarcoid I would think first of lupus miliaris But in Negroes I have been fooled many times by the clinical appearance, a case would appear to be one of lupus miliaris, and then the section would show typical sarcoid structure As far as a possible anergy is concerned, one can find cases of typical sarcoid in which strangely enough there is not a positive anergy If the combination of lupus vulgaris and sarcoid exists in the same patient, one can find a positive tuberculin reaction near the lupus vulgaris and a negative reaction near the sarcoid

DR FRED WISE The tuberculin reaction, which is negative in most sarcoid eruptions, is important in differentiating sarcoid from miliary tuberculosis

DR WILBERT SACHS No, it is the miliary type of sarcoid The tuberculin reaction is the same

DR JACK WOLF The small nodular lesions grouped around the nose often show the histologic picture of lupus vulgaris, especially in Negroes However, with the characteristic histologic picture of sarcoid and with the negative tuberculin reaction, I find no reason for not accepting the diagnosis of sarcoid

DR ARTHUR B HYMAN (by invitation) On the basis of the tuberculin reaction alone, it is impossible to distinguish between lupus miliaris disseminatus and sarcoid, because in both diseases there is a positive anergy, in most cases Sarcoid has been called disseminated miliary lupoid However, many conditions are neither miliary nor disseminated, but the term lupoid is more satisfactory than sarcoid The lesions show an attempt at pedunculation, because the skin of the eyelids is so thin that the lesions can grow only outward

DR ANTHONY C CIPOLLARO The term miliary lupoid does not appear in the Standard Nomenclature This disease is called tuberculosis miliaris disseminatus faciei and is described under sarcoid It is well established that tuberculin reactions are not diagnostic of the presence of tuberculins, and, therefore, in any individual case they cannot be utilized for differentiating the sarcoids from the true tuberculodermas

DR DAVID BLOOM This picture of raised, globular tumors attached to the skin with small surface is unusual for sarcoid or cutaneous tuberculosis, as it is so frequently seen in the Negro Therefore, when I first saw the patient I also considered the diagnosis of neurofibromatosis

DR WILBERT SACHS Do you remember whether one of the pedunculated lesions was removed?

DR ARTHUR B HYMAN (by invitation) No lesion was removed from the eyelids

Tuberculosis Cutis Colliquativa Satisfactory Response to Calciferol Therapy Presented by DR NATHAN SOBEL

Dystrophia Unguium (Psoriasis of the Nails?) Presented by DR FRED WISE

Pityriasis Rubra Pilaris, with Unsatisfactory Response to Vitamin A Therapy Presented by DR GEORGE C ANDREWS

Lymphangioma Circumscriptum Presented by DR DAVID BLOOM

B T, a girl aged 6, was registered at the Skin and Cancer Unit on Dec 30, 1946. She had an eruption on the right cheek extending to the right upper lip. According to her mother, this has been present since the age of 3 months.

On the right cheek, near the angle of the mouth, there is a close aggregation of lesions appearing as erythematous, hardly raised papules, assuming a somewhat roundish configuration $1\frac{1}{2}$ inches (4 cm) in diameter. The eruption extends in a thin line to the right side of the upper lip and stops sharply in the middle. The patient is presented for therapeutic suggestions.

DISCUSSION

DR NATHAN SOBEL I would either try desiccation or leave the lesion alone until the patient is 16 or 18 years old, and then consider plastic surgery.

DR JACK WOLF I am in favor of solid carbon dioxide.

DR ANTHONY C CIPOLLARO I agree with the use of carbon dioxide.

DR GEORGE C ANDREWS I think that it would be difficult for a plastic surgeon to do anything for this lesion, even at the age of 18. With the distribution on the cheek and the large area involved, it would probably result in even greater deformity. The trouble with desiccation is that the lesions tend to recur.

DR FRED WISE This form of circumscribed lymphangioma is extremely resistant to all forms of therapy. I would like to inquire whether any degree of success has been achieved with radium therapy.

DR ANTHONY C CIPOLLARO Few men have had much experience in the treatment of lymphangioma circumscriptum with radium. The disease is not rare, yet it is not sufficiently common to give any one much experience in its treatment. From the published articles on the use of radium and roentgen rays in the treatment of lymphangioma circumscriptum, I have the impression that ionizing radiations are not effectual in conservative dosage. It is possible to stop lymph flow with roentgen rays or radium, but the dosage would be so great as to produce permanent and harmful radiation changes. Therefore, I favor the conservative method of treatment with solid carbon dioxide. If it is used properly and conservatively the lesion will probably improve, with little or no deformity.

DR WILBERT SACHS If this is a deep lesion, I believe that the results will be unsatisfactory, regardless of therapy. However, if this is a superficial lesion, I would use Dr Rosen's suggestion. Instead of desiccation, I would use actual cautery. If one takes the actual cautery, tries it on a tongue depressor and uses it when it gives only the faintest tan, not charring, there will be no scar and no sequelae. This will be effective if the lesion is superficial.

DR DAVID BLOOM I feel that plastic surgery would possibly yield the best results. The thin lesion on the upper lip could be excised and the wound allowed to heal per primam. Then the larger lesion on the cheek could be treated. The task is to get as good a cosmetic result as possible in this girl.

DR WILBERT SACHS I think that it is analogous to angioma. There are too many lymph vessels. If they are dilated and superficial, it should not be difficult to handle.

DR DAVID BLOOM If plastic surgery is employed, would it be preferable to do it now or later when the girl is older?

DR WILBERT SACHS Now

Rodent Ulcer and Multiple Epitheliomas of the Face Presented by DR FRED WISE

W R, a man aged 57, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb 11, 1947, complaining of cutaneous lesions of eighteen months' duration. The patient gives a history of having had six roentgen treatments, of 1 unit each, about January 1946. Two months later an ulcer developed on the left side of the cheek.

On the left side of the upper lip, extending into the cheek almost to the floor of the orbit, and outwardly to the lateral limit of the malar bone, is a deep, penetrating, pear-shaped ulcer 6.25 cm in length and 5 cm in width, going through the full thickness of the upper lip and cheek and exposing the gum of the upper jaw. Induration is felt all along the edges of this ulceration, ranging from a few millimeters to about 1 cm in thickness. There is a lesion, also oval, located on the right temporal region, consisting of an ulcer that measures 4 by 2.9 cm, covered for the most part by a thick, greenish, irregular, adherent crust. This, too, shows some induration along its borders and considerable scarring, especially downward and backward from the main lesion. It is still slightly movable on the deep tissue. There are also several similar pea-sized lesions on the posterior portion of the right cheek.

The reactions to the Mazzini, Kline and cardiolipin tests were negative.

NOTE—The patient was referred to the Tumor Clinic of the Skin and Cancer Unit. He was seen by Dr Zimany, who advised wide removal of the whole area, including the bone, and said that the patient would have to wait two years to have the large defect in his face repaired.

DISCUSSION

DR ARTHUR B HYMAN (by invitation) When epithelioma invades the bone, do roentgen rays aggravate the process?

DR. GEORGE C ANDREWS Many authorities show excellent results with roentgen rays where there is involvement of bone. Roentgen rays should not be withheld, but should be given in high voltage, heavily filtered.

DR ANTHONY C CIPOLLARO This type of case, it seems to me, should be handled by radical operation. I am not opposed to chemosurgery, but it will not repair the defect already present. Chemosurgical treatment would probably arrest the neoplastic process, but then plastic surgery would be required to repair the damaged tissues. An extensive case like this is not one to be handled by a dermatologist.

DR WILBERT SACHS In this type of lesion, undoubtedly cancer cells are far from the lesion. The plastic surgeon, or anyone else, has no way of determining how far they have spread. Chemosurgery will tell that and will hunt out all cancer cells. After that, the patient may need plastic surgery.

DR. GEORGE C ANDREWS I agree with Dr Sachs.

DR FRED WISE The chemosurgical procedure recently described by Dr Moehs of Wisconsin seems to be especially applicable to this patient's lesions.

A Case for Diagnosis (Atrophic Lichen Planus?) Presented by DR JACK WOLF

METROPOLITAN DERMATOLOGIC SOCIETY

Leslie P Barker, M D , *President*

Thomas Graham, M D , *Secretary*

April 15, 1946

Mosaic Warts Presented by DR. ROYAL M MONTGOMERY

Ainhum Presented by DR ROYAL M MONTGOMERY

Parapsoriasis Presented by DR JOSEPH C AMERSBACH

A Case for Diagnosis (Atrophic Lichen Planus?) Presented by DR J LOWRY MILLER

W W, aged 34, a Cherokee Indian, was first seen at the Vanderbilt Clinic April 4, 1946, complaining of a vesicular dermatitis which has appeared each August for the past twenty years on the lower half of the legs. The lesions gradually disappear by winter, leaving pigmentation and infiltration. The patient has never noticed lesions on any other part of the body, except that the toe nails have never been normal. His general health has been good except for recent symptoms of a gastric ulcer.

Examination shows the legs to be covered with a mosaic pattern of active and inactive lesions from the midline between the knee and ankle down to the ankle. The active lesions are pea-sized to larger, violaceous, elevated, flattened plaques varied in shape. The inactive lesions are similar in size and shape and are elevated, the surface appears atrophic, but on palpation the individual lesions feel firm to the touch. On the shins are pigmented areas obviously sites of previous lesions. The toe nails are all deformed, thickened in places and totally missing in the middle third of several nails. General physical examination is normal. The teeth are normal, but the gums are swollen and bleed easily.

The Wassermann reaction of the blood was negative. A biopsy showed atrophy of the epidermis with a sclerodermatous infiltration underneath. No evidence of lichen planus was found.

DISCUSSION

DR A BINDER (by invitation) The fact that this eruption always begins in the summer and clears up in winter makes me think of the hydroa group of summer eruptions. However, it is unlikely that at this present age the patient should still exhibit such an eruption. It would be interesting to test him for porphyrins at the height of his eruption, but the absence of porphyrins would not rule out a hydroa eruption. The patient does not show any evidence of necrosis or scarring. The maldevelopment of his teeth and the dystrophic condition of his nails would seem to fit in with a congenital ectodermal defect which may account for the entire picture.

DR ROYAL M MONTGOMERY I do not know the diagnosis There are atrophic areas on the knees and elbows I wonder whether it is not related to acrodermatitis chronica atrophicans

DR JUAN LARRALDE (by invitation) This is the most unusual case that I have seen It seems to me that the condition can be placed among the congenital defects, although the features are atypical because of the normal hair and the dental development The atrophy of the skin over the knees as well as the changes in the toe nails make the picture rather suggestive of such a condition

DR JOSEPH C AMERSBACH I am inclined to agree with Dr Larralde about the main picture presented in this case It may be because of the underlying defects that exist in the skin that the hydra-like symptoms arise at certain times of the year

DR J LOWRY MILLER A biopsy showed superficial atrophy with scleroderma-like lesions underneath It is difficult to fit that in with the diagnosis of congenital defect The toe nails fit in with the latter The anterior portions of the leg certainly resemble remains of infected lesions, but the mosaic pattern presented on the back of the legs is unlike anything I have seen before I do not believe that it is acrodermatitis atrophicans One sees changes on the knees and elbows suggesting the parchment-like skin seen in cutis hyperelastica, but the other features of this disease are missing I am still at a loss for the correct diagnosis

Macular Atrophy. Presented by DR J LOWRY MILLER

Psoriasis Presented by DR ROYAL M MONTGOMERY

Secondary Syphilis Presented by DR J LOWRY MILLER

Leukotrichia Annularis Presented by DR ROYAL M MONTGOMERY

Leslie P Barker, M D, *President*

Thomas Graham, M D, *Secretary*

New York, May 20, 1946

Melanocarcinoma of the Foot with Inguinal Adenitis in a Woman Aged 69 Years Presented by DR JOSEPH C AMERSBACH

A Case for Diagnosis (Melanoma? Hemangioma? Pyogenic Granuloma? Histiocytoma?) Presented by DR LESLIE P BARKER

Erythroplasia Presented by DR LESLIE P BARKER

Dermatomyositis. Presented by DR ROYAL M MONTGOMERY

Epidermolysis Bullosa. Presented by DR J LOWRY MILLER

Leukotrichia Presented by DR J LOWRY MILLER

A Case for Diagnosis (Sarcoid Follicular Type?) Presented by DR J LOWRY MILLER

Ainhum in a Cuban Negro Presented by DR ROYAL M MONTGOMERY

Leslie P Barker, M D, *President*

Thomas Graham, M D, *Secretary*

Nov 18, 1946

Erythema Nodosum, Undulant Fever Presented by DR JOSEPH C AMERSBACH

Extensive Xanthoma of the Eyelids Presented by DR J LOWRY MILLER.

A Case for Diagnosis (Subacute Disseminated Lupus Erythematosus? Dermatitis Medicamentosa from Gold Sodium Thiosulphate?) Presented by DR J LOWRY MILLER

A Case for Diagnosis (Lupus Erythematosus?) Presented by DR J LOWRY MILLER

Pemphigus Erythematosus (Senear-Usher) Presented by DR J LOWRY MILLER

Leslie P Barker, M D, *President*

Thomas Graham, M D, *Secretary*

Jan 13, 1947

Acrodermatitis Chronica Atrophicans, Myxedema Presented by DR ROYAL M MONTGOMERY

Atypical Lupus Erythematosus of Arm, Late Stage Lupus Erythematosus of Neck Presented by DR JOSEPH C AMERSBACH

W K, on examination, showed erythema of the face with numerous hyperkeratotic areas and some atrophy on the cheeks. On the anterior aspects of both arms are similar atrophic areas with bands of erythematous infiltration. The palms and soles show a diffuse finely stippled erythematous eruption. The dorsal surfaces of the hands are erythematous and tender. The scalp and mouth are normal.

Hypertrophic Lichen Planus Presented by DR ROYAL M MONTGOMERY

Fox-Fordyce Disease in a Negro Woman Aged 26 Presented by DR LESLIE P BARKER

Nevus (Intracutaneous with Secondary Infection) Presented by DR JUAN LARRALDE for therapeutic suggestions

A Case for Diagnosis (Early Tertiary Syphilis?) Presented by DR J LOWRY MILLER.

Necrobiosis Lipoidica Diabeticorum Presented by DR J L MILLER

Chronic Arsenical Exfoliative Dermatitis Successfully Treated with 2, 3-Dimercaptopropanol (BAL) Presented by DR LESLIE PATTON BARKER

Kaposi's Varicelliform Eruption (Systemic Herpes Simplex) Presented by DR LESLIE PATTON BARKER

Leslie P Barker, M D, *President*

Thomas Graham, M D, *Secretary*

Feb 10, 1947

A Case for Diagnosis (Parapsoriasis?). Presented by DR J LOWRY MILLER

A Case for Diagnosis (Seborrheic Dermatitis? Psoriasis?). Presented by
DR JUAN LARRALDE

Neurotic Excoriations in a Patient with Psychoneurosis Presented by
DR LESLIE P BARKER.

Boeck's Sarcoid, Extensive Involvement of Face, Neck and Arms Pre-
sented by DR J LOWRY MILLER

Leslie P Barker, M D, *President*

Thomas Graham, M D, *Secretary*

March 17, 1947

A Case for Diagnosis (Lupus Miliaris Disseminatus Faciei? Rosacea-
Like Tuberculid of Lewandowsky?). Presented by DR J LOWRY MILLER.

Erythroplasia of Queyrat with Epitheliomatous Changes Presented by
DR ROYAL M MONTGOMERY

E W, a man aged 42, has had an irritation, with itching, on the glans and
prepuce for years. He has had a verrucous nodule on the glans for about one year.

Thirteen months ago, the patient reported with an infected prepuce and phimosis.
He was advised to have a circumcision. This was performed one year ago. Two
months later the patient had a superficial ulcer on the tip of the glans and a small
verrucous nodule in the sulcus on the dorsal side. The glans was red and macerated
at the time.

At the present time the glans is erythematous and oozing. A scale develops
at this site if a soothing ointment is not applied. The area immediately around
the meatus is normal, however, the area to the lateral sides seems indurated.
There is a painful fissure in the sulcus on the right side. On the dorsum of the
penis in the sulcus there is a horny nodule about 0.7 cm in diameter. This is
attached to the skin. There are no palpable glands in the inguinal areas.

The Wassermann reaction of the blood was negative.

DISCUSSION

DR THOMAS N GRAHAM: I think that this lesion corresponds clinically to
erythroplasia of Queyrat. The question arises whether or not these cases corre-
spond to those described in the French literature, in most of which highly malignant
changes developed. In the majority of the cases which we have seen the lesions
have not undergone those changes. Studies of sections should be of value in
interpreting the condition.

DR J LOWRY MILLER: I think this is unquestionably erythroplasia with
epitheliomatous changes. A biopsy is indicated, to be followed as quickly as

possible by amputation of the penis. Probably resection of the draining glands will not be necessary. I do not think that any other type of therapy should be attempted at the present time.

DR LESLIE P. BARKER. I think this is an extensive case of erythroplasia, but two areas already show clinical evidence of epitheliomatous degeneration.

DR ROYAL M. MONTGOMERY. Dr Wilbert Sachs has recently reported about 10 cases of erythroplasia in which he claims to have obtained good results with local application of a neoarsphenamine solution. I wonder if it would not be worth while to use this on the area of erythroplasia. If the nodule proves to be squamous cell epithelioma, he will undergo a radical amputation.

A Case for Diagnosis (Fibroma? Glossitis Rhomboidea Mediana?) Presented by DR THOMAS N. GRAHAM

A Case for Diagnosis (Dermatitis Faciæ, Actinomycosis?) Presented by DR THOMAS N. GRAHAM

MINNESOTA DERMATOLOGICAL SOCIETY

Louis A Brunsting, M D , *President*

Rodney F Kendall, M D , *Secretary*

Sept 15, 1946

The following 31 cases were presented by Doctors Paul A O'Leary, Hamilton Montgomery, Louis A Brunsting and Robert R Kierland, at Rochester, Minn

Favus of the Scalp.

E V , a 13 year old girl, shows scattered patches of crusting of the scalp of nine years' duration The eruption has spread slowly, and recently areas of permanent alopecia have developed A variety of topical applications has had no influence on the course of the disease The father stated that his two brothers had a similar condition and that they subsequently had severe scarring of the scalp with practically total loss of hair The father's uncle was also known to have a similar disease The patient's sisters are described as having had the same disease, with spontaneous cure, but there is no knowledge as to their present status These persons are all American born, of Dutch descent

Scattered over the scalp are pea-sized to dime-sized, thick, greasy, yellow crusts These crusts when removed leave a bleeding base There are several coin-sized areas of scarring and atrophy with alopecia The scalp has a distinctive mousy odor Infected hairs fluoresce under Wood's light Cultures of the hair are positive for *Trichophyton schoenleinii* The hair has been subjected to roentgen epilation, which is to be followed by manual removal of the remaining infected hairs

Moniliasis; Extensive Trichophytosis of the Glabrous Skin

J A , a 19 year old youth, has had severe stomatitis with involvement of the buccal membranes, tongue and lips, and also perlèche since the age of 6 At the age of 13 years, fissuring and scaling of the skin appeared between the toes of the left foot and there was a gradual spread upward to involve both feet, ankles and legs to the middle part of the thigh Fourteen months ago similar lesions appeared on the dorsum of the left hand, which had spread two thirds of the way up the forearm in typical gauntlet distribution This eruption has remained about the same during the period of one year of observation

In the mouth there are numerous whitish confluent plaques on the mucosal surface of the tongue and lips and extending beyond the mucocutaneous border to the glabrous skin around the mouth There are deep fissures at the corner of the mouth and on the upper surface of the tongue Both feet are covered with severe crusting erythematous scaly lesions which are almost completely confluent The borders of the lesions are circinate, elevated and studded with pinpoint vesicles The toe nails are greatly thickened, friable and dystrophic The soles are extremely hyperkeratotic Results of all cutaneous tests for *Trichophyton* and *Oidiomycin*

organisms are negative. Cultures of the mouth, tongue and stool are positive for *Candida albicans*. Cultures of the legs, feet and toe nails are positive for *Trichophyton purpureum*.

Moniliasis, Generalized Favus of the Scalp and Glabrous Skin

A H, a 10 year old girl, has had severe generalized dermatitis and stomatitis for seven years. At the age of 3, at the same time that typical ringworm developed in other children in the neighborhood, the patient had half-dollar-sized, red, scaly plaques on the legs. These lesions were refractory to treatment and remained localized for about one year. Subsequently there was a gradual spread to involve first the thigh, and then the rest of the body. Mild persistent diarrhea developed. Four and one-half years ago, the patient had erosive lesions of the mouth and abscesses on the buttocks with a febrile reaction. Three years ago the patient had a severe generalized exanthematous reaction, with swelling of the face and mouth, which subsided in two to three weeks leaving crusted erythematous plaques over the body and legs. One and one-half years ago the face and scalp became involved, and since this time the patient has had progressive, relatively complete alopecia with scarring of the scalp. The nails have become dystrophic, friable and hyperkeratotic. The patient has had a succession of lesions on the body which spontaneously cleared, only to be followed by the formation of new crusts. The patient has had a low grade fever for an indefinite period.

Generalized on the scalp, face, trunk and extremities are multiple erythematous rupioid lesions. There is almost complete alopecia of the scalp. About the nose and chin there are numerous rupioid and verrucoid lesions that are black. About the mouth the lesions are erythematous and eczematoid. At the corners of the mouth are deep fissures. The mucous membranes of the mouth and tongue are covered with white plaques. On the body and proximal portions of the extremities are numerous coin-sized to palm-sized circinate lesions with elevated erythematous borders and scaling centers. On the knees, ankles, wrists and hands there are massive rupioid lesions with hyperkeratotic and exudative crusts. The patient has a distinctive mousy odor. The scalp is fluorescent under Wood's light. Fungi have been found in all lesions of the scalp, face, body and extremities characteristic of a dermatophyte. Budding cells and filaments typical of *Candida albicans* are present in the lesions of the mouth. Reactions to cutaneous tests with Oidiomycin and Trichophyton (commercial) and autogenous extracts of *Microsporum canis* and *Candida albicans* are all repeatedly negative in several dilutions. Cultures of the mouth and stool are positive for *Candida albicans*. Cultures of all the other areas are positive for *M. canis*.

Actinomycosis and Tuberculosis

D C, a 36 year old man, was in good health until nine months ago, when he noted a boil on the inner aspect of the right thigh, which failed to heal after being lanced. New lesions appeared in the suture line after surgical incision elsewhere. Low grade fever, loss of weight and progressive weakness have persisted. One month ago a nodular lesion appeared on the right arm. Treatment with sulfonamide drugs appeared helpful in the early stages of the disease.

On the medial aspect of the right thigh there are clusters of necrotic ulcers with a deep firm indurated base. On the right arm at the point of insertion of the deltoid there is a quarter-sized erythematous nodule. A roentgenogram of the thorax revealed confluent pneumoconiosis, an inflammatory process in both upper lobes and a diffuse nodular infiltration of the fields of both lungs consistent

with a diagnosis of milary tuberculosis. The sedimentation rate of the erythrocytes was elevated. Biopsy of an enlarged, left supraclavicular node revealed tuberculosis, this was confirmed by guinea pig inoculation. Culture of the lesions in the right groin and on the right arm yielded a pure culture of *Nocardia aureus*.

Blastomycosis with Cutaneous, Scrotal and Prostatic Involvement.

H L., a 39 year old man, had five coin-sized lesions on the face three and a half years ago, which gradually enlarged and coalesced to form a palm-sized lesion encompassing the left eye, temple, cheek and maxilla, with destruction of the skin of the orbit. Four months ago there was noted swelling of the left side of the scrotum with subsequent formation of a warty lesion on the skin in this area. Cultures taken from the lesions on the scrotum and face were positive for *Blastomyces dermatitidis*. Cultures of the urine were positive for blastomycetes, and subsequent attempts to determine the point of origin of the positive urine cultures demonstrated the prostate to be the source of infection. The disease process in the face and scrotum has responded well to treatment consisting of the use of roentgen rays, potassium iodide by mouth and a course of injections of autogenous vaccine, but the prostatic secretion still reveals blastomycetes in pure culture.

DISCUSSION

DR REUBEN NOMLAND, Iowa City. I would like to ask whether it was the father or the grandfather who had the wig, and whether he had had favus. I think that practically all cases of favus that are found in young persons in America are found in the second and third generations. Several such groups have been observed in Chicago particularly. In the second and third cases, without cultural studies one would have assumed that the cutaneous lesions were caused by *Monilia* organisms. I am sure that *monilia* in the skin can produce an eruption exactly like the cutaneous lesions that were present in both cases.

DR FRANCIS LYNCH, St Paul. Perhaps Dr DeLamater will give his opinion as to the absence of reaction to cutaneous tests in cases 2 and 3, particularly since in case 2 there is a papular eruption on the chest, apparently an id.

DR STEPHAN ROTHMAN, Chicago. In cases 2 and 3 a lack of defense or increased susceptibility is obvious, in view of persistence of the infection, recurrences over a period of years, unsatisfactory response to therapy and negative cutaneous reactions to vaccines. I know of 1 case in which the cause of generalized intractable cutaneous moniliasis could be found in an atypical disturbance of the carbohydrate metabolism, which in turn was due to a pancreatic carcinoma (S W Becker, D Kahn and S Rothman. *ARCH DERMAT & SYPH* 45 1069-1080 [June] 1942). At present I have another patient under observation with generalized cutaneous moniliasis, who has a slightly decreased glucose tolerance and alimentary glycosuria. The little girl (case 3) is apparently ill from dissemination of *Monilia* into internal organs. But in the boy's case (case 2) in which moniliasis and fungous disease are limited to the skin and mucous membranes, some unusual metabolic disturbance must be assumed and sought for.

DR E D DELAMATER, Rochester, Minn (by invitation). The first case of favus is presented to emphasize that this is the third generation in which this disease has occurred in this family. This represents the fourth generation of this family in this country. We do not know whether the great-grandparents brought this disease from Holland, but there is a fairly good suspicion. At the present time the father still presents evidence of having had the infection as a young man, for he is practically bald as a result of extensive scarring of the scalp, such as

is characteristic of the end result of this disease. The child at the present time presents a fairly characteristic picture of favus, except that many of the crusts or scutula which were visible several weeks ago have been removed by the falling of the hair as a result of roentgen therapy.

Case 2 and case 3 rightfully should perhaps be discussed together because they both are examples of concurrent infections with *Candida albicans* and one of the dermatophytes. In both cases the degree of moniliasis and dermatophytosis is severe. The moniliasis in both cases is characterized by severe stomatitis with the formation of white membranes on the tongue, gingivae and the inner surfaces of the cheek. There is also severe perleche. In both cases *Candida albicans* can be grown in vast numbers from the stool. In case 2, that of the young man, the dermatophytosis is due to *Trichophyton purpureum*. The disease involves both feet, legs and parts of the thighs, and there is almost a complete destruction of all the toe nails. Where the crust is not too heavy the annular character of the lesions is apparent. It is interesting that a third organism has been consistently isolated in all cultures taken from the feet and the legs. This is a species of *Geotrichum*. Whether this organism adds to the clinical picture or is simply growing as a saprophyte in the lesions is not clear. Also, there has been considerable variation in the *Trichophyton* organisms isolated in this case. Some of the specimens produce no pigment whatsoever, being fairly characteristic of *Trichophyton niveum*, while others produce large amounts of pigment and are fairly characteristic of *T. purpureum*. Interpretation of these cultures is difficult and must be based on knowledge of the wide range of variation that is observed in these organisms as occurring spontaneously, as well as on the observations of Dr. Emmons, who has produced numerous mutants by exposing cultures of *Trichophyton* on organisms to ultraviolet rays. It is felt that the production of pigment is probably dependent on a mutation or variation.

The third case is that of a young girl who has severe gastrointestinal moniliasis and concurrent favus produced, curiously enough, by *Microsporum canis*. This case emphasizes dramatically the fact that organisms other than *Trichophyton* (*Achorion*) *schoenleini* can produce true clinical favus on rare occasions. In both this case and the previous case there is no reaction to either commercial or autogenous fungous extracts, and the inflammatory process in the lesions of both is minimal, which are indications of a negative anergy and a lack of immunity. These cases parallel the case reported by Lamb and Hazel several years ago, which was also thoroughly studied in the department of dermatology at Columbia University. On the basis of our ignorance on the subject of severe concurrent fungous infections the prognosis in both of these cases does not appear to be good.

The fourth case represents a man with an infection due to an unusual strain of aerobic *Actinomyces*, usually classified as *Nocardia*. It was felt, when this fungus was first isolated in pure culture from the lesions on the arm, that it probably was *Nocardia asteroides*, however, it presents certain features which are not characteristic of this organism. The same organism was isolated elsewhere, prior to the patient's coming to our clinic, and cultures of these specimens are found to be identical with those made at Mayo Clinic. In general, concerning the treatment of actinomycosis, it may be said that *Actinomyces bovis* is more susceptible to penicillin, whereas the aerobic nocardias are more susceptible to sulfonamide drugs. This organism has been tested in our laboratory and found to be at least partially susceptible to the sulfonamide drugs, so that the prognosis so far as the actinomycosis is concerned may be good. The patient also has concurrent military tuberculosis, which may well prove fatal.

Concerning the man with blastomycosis, there were typical lesions of the skin as well as evidence of systemic involvement. This is the second instance in the last three months in which we have isolated the organism from the urine. On several occasions we have been able to demonstrate that the prostate is the focus of infection in the urinary tract. It may be pointed out that in numerous cases reported in the literature, blastomycetes have been isolated from the urine. Inasmuch as this man has spent much of his spare time while receiving treatment visiting the roundabout county fairs, it occurred to me that, in this way, he might be seeding the ground in various rural communities. With this in mind, we planted the organism from this patient, as well as other strains of *Blastomyces*, on sterilized garden dirt and found them to grow readily in the typical mycelial phase.

I do not feel at the moment that I am in a position to discuss folic acid in the treatment of sprue, however, there have been several reports in the recent literature concerning its efficacy in this disease. It is planned that as soon as a sufficient quantity of this drug is obtained for the purpose, the patients in case 2 and case 3 will be treated with it. I can only guess whether by this means the gastrointestinal infection due to *Candida albicans* will be eliminated. If effective, what bearing the elimination of one disease will have on the course of the generalized severe ringworm in each case will be interesting to observe.

Mycosis Fungoides

Mrs J C, a 54 year old white woman, was first seen in August 1946. Five years previously she had first had pruritus and erythema of the arms and neck, which was followed by a bullous eruption about the ankles. Ten months previously she began to have some thickening and exudation of the skin about the legs, thighs and abdomen. The pruritus has decreased, but the skin has never cleared entirely since the onset. The blood is normal except for eosinophilia and monocytosis. The sedimentation rate was 50 mm in 1 hour. Histologic examination revealed mycosis fungoides (back) and eczematoid dermatitis (abdomen).

Mycosis Fungoides, Toxic Erythroderma.

M F A, a 46 year old white widow, was first seen here Aug 29, 1945. The onset of her disease was one year previously, with the appearance of an asymptomatic scaling patch on the left thigh. Subsequent plaques developed into tumors and have been intensely pruritic. She has been hospitalized three times during the past six months for treatment of her cutaneous disease. During the past six months, universal erythroderma has appeared. The present as well as previous hospitalizations have been marked by frequent seizures of high fever, increased pulse rate, severe general malaise and edema of the face, feet and hands with an impetiginized crusted eruption. Treatment during the past year has consisted of fever and ethyl chaulmoograte therapy, roentgen therapy and penicillin therapy. There has been constant albuminuria. The sedimentation rate is steadily mounting. Severe secondary anemia has been treated with blood transfusions and ferrous sulfate. There were no significant changes in the peripheral blood. Histologic examination showed mycosis fungoides.

Mycosis Fungoides with Poikiloderma-like Changes

C F, a 58 year old farmer, was first seen at Mayo Clinic in 1937 with a dermatitis of twenty years' duration. A single "smooth brown" lesion appeared

on the thigh at 17 years of age, since then, there has been a gradual increase in the number and size of the plaques. Examination revealed numerous indurated scaling plaques with mottling and atrophy in areas. Three biopsies at this time showed varying features of mycosis fungoides. Roentgen therapy at varying intervals has afforded symptomatic relief. In 1942 a course of eight hyperthermal treatments was given. A biopsy specimen taken in June 1946 showed mycosis fungoides with poikiloderma-like changes. Examination now shows scaling, pigmentation, mottling and atrophy in association with the indurated plaques. The general health has remained good.

Mycosis Fungoides.

J H K, a 37 year old white man, was admitted to the Mayo Clinic for the first time on Feb 21, 1944, complaining of recurring, intensely pruritic plaques and tumors about the trunk and extremities. Onset was in 1942, with appearance of asymptomatic scaling plaques of the trunk. In 1943, these became pruritic. Roentgen therapy has been followed by resolution of these pruritic plaques. Brown-pigmented, macular areas mark the sites of former plaques and tumors. In April 1946, the patient was treated again for a tomato-sized tumor of the nose. Within a few weeks after roentgen therapy, the tumor had disappeared, and the present normal contours of the nose returned. The lesion of the left ankle has been present five weeks. Resolution has already begun since the first roentgen treatment a few days ago. There are no abnormal laboratory observations. Studies of smears of the peripheral blood reveal no evidence of lymphoblastoma. Histologic examination showed mycosis fungoides.

Erythroderma, Leukemic Reticuloendotheliosis (Monocytic Leukemia of Shilling)

J H F, a 53 year old white man, first noted an erythematous papular eruption of the inguinal regions in 1942. There has been a gradual spread to the entire body, accompanied with severe pruritus. Several years ago, he noted occasional circinate lesions and scattered rough plaques on the lower part of the abdomen. In 1945 the face, neck, palms and soles became involved. The pruritus is aggravated by heat and moisture. The weight has remained unchanged for the last six months. High and low voltage roentgen therapy was given in 1945 and 1946.

Physical examination reveals a well developed obese man. There is universal exfoliative dermatitis with purpuric elements apparent in the skin of the face, upper part of the trunk and extremities. There is generalized lymphadenopathy, but the spleen is not palpable.

Biopsy of skin and smears of peripheral blood reveal characteristic features of leukemic reticuloendotheliosis. Bone marrow obtained by sternal aspiration revealed occasional leukemic reticuloendothelial cells. The values for hemoglobin and erythrocytes were essentially normal. Leukocytes on four occasions were recorded as 17,000, 44,300, 82,000 and 19,000 cells per cubic millimeter, respectively. Thrombocytes numbered 44,000 per cubic millimeter on a recent examination. The differential ratio of leukocytes revealed leukemic reticuloendothelial cells, 41 per cent on one occasion and 24 per cent on another.

DISCUSSION

DR FRANCIS LYNCH. Erythroderma is a rare manifestation of monocytic leukemia, which has been called to our attention by Dr. Montgomery on several

occasions The purpuric tendency seen here is seldom met with in erythroderma of other causation and might be regarded as an aid in differentiation of the cause of the erythroderma since it is so often observed in leukemia cutis of any clinical form

DR. HAMILTON MONTGOMERY I am glad that Dr Lynch mentioned the purpuric features in this case In cases of monocytic leukemia especially of the Shilling type, whether the cutaneous manifestations are those of nodules and plaques or those of erythroderma, purpuric lesions occur early in the disease, in contrast to purpuric lesions occurring usually only in the terminal phases of other types of lymphoblastoma

Lipid Proteinosis.

L C, a farm hand aged 21, first was admitted to the clinic in January 1914 (Montgomery, H, and Havens, F Z Xanthomatosis IV Lipoid Proteinosis (Phosphatide Lipoidosis), *Arch Otolaryng* 29.650-661 [April] 1939) He complained of precordial pain of four months' duration He was found to have symptoms

Observations of Lipids in the Blood and Skin

Date	Blood Lipids (Mg /Cc)					Skin Lipids, Per-centage	
	2/10/33	4/13/33	8/24/33	1/14/41	2/1/43	4/13/46	4/15/38
Cholesterol	214	181	216		228	112	0 3
Cholesterol esters	166	146	152		134	89	0 3
Lecithin	181	253	227	101	253	262	1 5
Fatty acids	338	289	413		578	249	1 6
Total lipids	552	470	629		806	361	1 9
Total phospholipids				226			
Sphingomyelin				46			
Cephalin				79			

of exophthalmic goiter, and at operation a diagnosis of hypertrophic parenchymatous thyroid was made Examination at that time revealed the presence of stomatitis, pharyngitis, laryngitis and a peculiar bleblike formation over the tonsils In June 1915, the patient complained by correspondence that he had been losing his speech since the thyroid operation In 1920 he complained of continued hoarseness

In February 1938, at the age of 45, the patient returned to the clinic because the hoarseness had increased during the preceding six months and because the tip of the tongue had become sore Questioning revealed that hoarseness had been present since infancy, but had not been severe until recently and that he had had open sores on the buttocks as a child, lesions on the elbows and knees for twenty years, and lesions on the chin and mucocutaneous junctions for about two years The family history was noncontributory

In January 1941, on the patient's next admission to the clinic, his hoarseness had increased and he had difficulty talking for any length of time, he complained of a sensation of constriction about his heart following exertion or excitement

In January 1943, at his next visit to the clinic, he complained of soreness of the left side of the throat, which had been present for one year A small ulcer was found between the tongue and the left lateral pharyngeal wall

In September 1946, at the patient's most recent visit to the clinic, the hypopharynx and larynx were unchanged, but there was more infiltration of the margins of the epiglottis than before.

Tests made in 1938 showed glucose tolerance to be normal, blood sugar 90 mg per hundred cubic centimeters and basal metabolic rate—8 per cent, the result of the test of hepatic function was normal.

DISCUSSION

DR HAMILTON MONTGOMERY This patient first came to the clinic in 1914, at which time Dr Balfour performed a thyroidectomy for an exophthalmic goiter. He had had a little hoarseness before the operation. However, the hoarseness became much greater postoperatively, and the patient was inclined to believe that the hoarseness was a sequela to the operation. However, this man's hoarseness is due entirely to his lipid proteinosis. When we first saw this patient in 1938, we thought of localized amyloidosis or neurodermatitis, because of the total absence of yellowish hue to the lesions. The disease has not progressed appreciably since the time of first examination, except possibly by a little greater infiltration of the vocal cords. It is to be noted that his blood lipids have always been within normal limits except for a relative increase in phosphatides noted in the analysis done a couple of days ago. The cholesterol and total lipids are now considerably below normal. Similar observations in regard to blood lipids have been reported in cases since Dr Havens and I originally reported this case (*Arch Otolaryng* 29 650-661, 1939). In lipid proteinosis there is merging of the lipids with the connective tissue and deposition of lipids in the walls of the capillaries. No foam or xanthoma cells are present. One might regard this condition as a degenerative process rather than a true xanthomatosis.

DR STEPHAN ROTHMAN Like Dr Montgomery, we found in our case high phosphorus values in the diseased tissue, but normal blood lipid values, including phosphatides. The disease seems to be a genetically induced degenerative process rather than a metabolic disturbance.

Xanthoma Diabeticorum

E O, a 30 year old white man, was found to have diabetes mellitus in 1943 while in the army. He since has been able to control his diabetes fairly well with a weighed diet and 40 to 45 units of protamine zinc insulin daily. In January 1946, he changed brands of insulin. Within ten days he noticed the development of papules and nodules on the trunk, extremities and neck. Ten days later he changed back to the previous brand of insulin, and since then the cutaneous lesions have been subsiding. During the three to four months prior to his admission to the clinic, on Aug 20, he lost 30 pounds (Kg) in weight and noticed the onset of generalized fatigability, burning, numbness and weakness of the hands and muscular cramps in the legs at night. The patient's family history and systemic review do not reveal information of significance.

Examination reveals discrete pinhead-sized to bean-sized, pale red and violaceous nodules studded with yellow areas, similar nodules which are crusted and numerous excoriations on the trunk, extremities and neck.

Laboratory examination revealed the presence of sugar, acetone and diacetic acid in the urine. The fasting blood sugar level was 318 mg per hundred cubic centimeters. Blood lipid studies showed cholesterol, 812 mg, cholesterol esters 566 mg, fatty acids, 2,632 mg, lecithin, 734 mg, and total lipids, 3,144 mg per hundred cubic centimeters.

The histologic picture of tissue removed from a lesion on the patient's left knee was characteristic of xanthoma

Xanthomatous Biliary Cirrhosis (Burger and Grutz Cutaneous and Mucosal Lipoidosis?), Xanthoma Tuberosum, Secondary to Hepatic Disease (Obstructive Jaundice)

R N, a 50 year old unmarried white woman, was well until January 1942, when she had her initial attack of pain in the right upper quadrant of the abdomen and light-colored stools. In August 1942 a cholecystectomy was done, revealing cholelithiasis. Postoperatively she had pneumonia, anuria and decrease in weight from 120 to 85 pounds (54 Kg to 39 Kg) in two months. Surgical reconstruction of the common bile duct in October was followed within one month by onset of jaundice, which has persisted to date. In the latter part of 1942 there appeared yellow periorbital infiltrations. Between November 1942 and April 1944, there were attacks of chills and fever about every two weeks, ceasing after further surgical attention to the common bile ducts in April, since which time the stools have again been normal in color. Beginning in December 1944,

Results of Studies

	Blood Lipids (Mg /100 Cc)	Normal Values (Mg /100 Cc)
Cholesterol	508	150-250
Cholesterol esters	305	100-175
Phospholipids	1,136	185-250
Fatty acids	1,634	250-400
Total lipids	2,142	400-650
Bilirubin direct	13.3	Negative
Bilirubin indirect	2.1	0.6
Serum protein	8.4*	6-8.3*
Albumin globulin ratio	1.1/1	1.5/1-3/1

* These values are in grams per hundred cubic centimeters

yellow nodules appeared on the ears, elbows, knuckles and toes, with small plaques in the perioral wrinkle lines and the palmar folds of the fingers, and diffuse non-elevated yellow infiltrations periorbitally, periorally, on the neck, hard palate and buccal and gingival mucosa. There is no familial history of xanthoma. One brother died of heart trouble at the age of 50 years.

At present, the skin is intensely jaundiced, the liver edge is palpable across the epigastrium 1 fingerbreadth above the umbilicus. Small nodular infiltrations can be palpated on the extensor tendons of the arms and legs.

DISCUSSION

DR. REUBEN NOMLAND: Do you think that obstructive jaundice as such can produce xanthomatosis of the skin without producing biliary cirrhosis?

DR. CARL LAYMON, Minneapolis: It is indeed a privilege to see a group of lipoidoses such as those presented today. The female patient with xanthomatous biliary cirrhosis well exemplifies the point made by several observers that xanthomatous disease of the liver is rather frequently associated with lesions on the palms and soles.

DR. HAMILTON MONTGOMERY: This case is of considerable interest to me because the history and course of events is rather typical for xanthomatous biliary cirrhosis, yet, the patient has involvement of the corners of the mouth and large

plaque-like lesions similar to those in a case of more extensive involvement we had recently which seemed to fit in with Burger-Grutz hepatosplenomegaly with cutaneous and mucous membrane lipoidosis. In both these recent cases, there was great increase in phospholipids, over half of the total lipids in both cases being in this form. In the usual case of xanthomatous biliary cirrhosis, the major increase is in cholesterol, occasionally in free cholesterol rather than in cholesterol esters. The phospholipids are also increased, but not out of proportion to the total lipids. Burger and Grutz's first patient with hepatosplenomegaly and cutaneous and mucous membrane lipoidosis did not have jaundice. A second patient whom they reported did have jaundice. Both had a disproportionate elevation of phospholipids, and both showed decided response to dietary measures. In our cases, we were unable to break down blood lipids to monophosphatides and diaminophosphatides. In Niemann-Pick disease, there is decided increase in sphingomyelin or diaminophosphatides, and again there is hepatosplenomegaly. The prognosis in xanthomatous biliary cirrhosis, which I am afraid this woman has, is usually serious. She should, nevertheless, be on an animal-fat-free diet. Other remedies, such as lipocaic and choline, which have been advocated in xanthomatosis have not proved effective in our experience.

When cutaneous xanthoma occurs as a primary disease or secondary to hepatic disease, one is likely to find both xanthoma-tuberosum-like lesions occurring on extensor surfaces and lesions simulating xanthoma disseminatum occurring on the flexural surfaces. In the latter condition, there is no elevation of blood lipids, although the histologic picture of both is similar and both present typical xanthoma and Touton giant cells.

The picture presented by the patient with xanthoma diabeticorum is what Thannhauser would call the eruptive secondary type of xanthomatosis. A specimen from one of the excoriated lesions is typical of xanthoma, but already there is partial absorption of the lipids by the reticuloendothelial system in response to treatment. In xanthoma diabeticorum, the fatty acids are increased out of all proportion to the other blood plasma lipids and the cutaneous lesions respond quickly to a diabetic regimen, including the administration of insulin.

Pseudo Xanthoma Elasticum

J S., a 25 year old white woman, an x-ray technician, was first seen here in March 1945, for diagnosis of yellowish discolorations of the flexural areas of the body. A small lesion was first noticed on the right side of the neck about fifteen years ago. This gradually enlarged, but did not cause her concern until about two years ago, when lesions began appearing elsewhere. Since then the plaques have gradually increased in size. Lesions have been symptomless. She knows of no similar cutaneous disease in her family. The ophthalmologist found typical angioid streaks of the retinas around the optic disks. Visual acuity has decreased greatly in the last two years.

Examination reveals rather extensive linear discolorations on the sides of the neck, axillas, flexor surfaces of the arms, groins and popliteal regions. The individual lesions are small circumscribed cream-colored to yellow nodules which coalesce to form streaks. The skin in the affected areas is relaxed and loose, forming folds.

DISCUSSION

DR REUBEN NOMLAND: The thing I wish to discuss about the patient with pseudoxanthoma elasticum is the micromincination of the skin. Several years ago Dr. Clark Finnerud and I, in 2 cases of pseudoxanthoma, found that there

was a great increase in calcium salts which outlined the degenerated elastic tissue fibers. The increased calcium was shown by chemical analysis and by special stains for calcium. I do not believe that the presence of calcium is of special significance, as it is deposited in degenerated tissues, a phenomenon that is found in many pathologic processes.

Epidermolysis Bullosa, Colloid Milium

R. H., 20 year old farmer, complained of recurring episodes of water blisters on his hands since June 1946. Bullae, sometimes with hemorrhage, varying in number from two to six, appear after a hard day's work. They arise from apparently normal skin, do not itch and last for several days. When he does not work, there are no bullae. Thickening of the distal fourth of his nose has been present for six months. His past history is essentially normal save that for six weeks in the summer of 1945 similar lesions were present. There is no history of atopy, intake of drugs or familial cutaneous disease.

Four to five bullae are present at the lateral and dorsal surfaces of the fingers and hands. A few scattered excoriated lesions are present on the posterior surface of the neck. The distal fourth of his nose is lichenified, and there are small verrucous lesions. Tinea versicolor is present on his trunk and upper extremities. Results of laboratory studies are essentially normal. A single specimen of urine revealed no evidence of primary fluorescence, and the reaction to the test for porphobilinogen was doubtful. Results of photosensitivity studies were negative, as were results of patch tests with suspected farm contacts. Microscopic sections of the skin of the nose revealed features of colloid milium.

DISCUSSION

DR STEPHAN ROTHMAN: What spectral regions were used in testing the light sensitivity in this case? Unfortunately, our knowledge of hydroa aestivale and of its range of light sensitivity is rather incomplete. There are clinically typical cases, some with and some without porphyria. Abnormal light sensitivity sometimes was found in the short wave ultraviolet region (for instance by Martenstein), whereas porphyrins sensitize in the region of 4,000 angstrom units.

DR LOUIS A. BRUNSTING: The skin was tested in various ways, including with visible and with ultraviolet rays. We suspected porphyria but could not prove it. (Subsequently there developed abdominal symptoms of acute porphyria with port-wine-colored urine which contained large amounts of coproporphyrin and uroporphyrin. The patient's mother was found to have latent porphyria.)

Acne Conglobata.

Mrs. C. A. K., 43 years old, farmer's wife, has had chronic small superficial granulomas on her body for thirty-five years. The lesions began as papules, which enlarge peripherally to form an indurated purplish red plaque with two or three sinuses which exude seropurulent material. The lesions resolve slowly in four to six months, leaving a slightly depressed scar. One year ago, a similar lesion appeared on the left buttock, with gradual increase in size and severity until now most of the buttock is involved by a large granulomatous mass.

Since July 1946, she has had intermittent nausea and vomiting, numbness of the hands and feet, weakness of the arms and legs and mild ataxia. It is for the latter symptoms that she seeks medical care.

The general physical examination reveals extensor muscle weakness of the arms and legs, loss of vibratory sense of the legs, a positive Romberg sign and

mild ataxia. It is the opinion of the neurologist that these signs are those of a Guillain-Barre syndrome.

Laboratory studies reveal an elevation of the sedimentation rate of the erythrocytes, mild hypochromic secondary anemia with moderate leukocytosis and a positive reaction to the Nonne test of the cerebral spinal fluid with a total protein of 70 mg per hundred cubic centimeters. Cultures from the left buttock grew gram-negative and gram-positive bacilli, *Streptococcus hemolyticus*, *Aerobacter aerogenes* and *Escherichia coli*. Cultures of the lesions and spinal fluid were negative for fungi.

Hidradenitis Suppurativa

H J J, a 47 year old police officer, first noted furuncles in the left axilla ten years ago. These lesions were followed by chronic inflammatory nodules, draining sinuses and formation of corded scar tissue. Two years later, the right axilla, the groins, the perianal areas, the gluteal cleft and the adjacent areas of the buttocks became involved by the same process, which has steadily increased in severity and extent. The general health has not been affected. Laboratory studies reveal only mild hypochromic secondary anemia. Cultures revealed a growth of *Staphylococcus aureus*.

Hidradenitis Suppurativa

L B, a 22 year old Negro woman was first seen in November 1945. At the age of 17, draining furuncles of the sternal region developed, which healed completely after four years. At 18 years of age, she noted multiple abscess formation with sinus tracts about the pubic, vulvar and perianal areas, which has continued in spite of much treatment. For three and a half years there has been decided edema of the vulva.

Laboratory examinations revealed moderate secondary anemia. The sedimentation rate was 120 mm in 1 hour. Biopsy and scraping from the lesions repeatedly failed to reveal Donovan bodies. Repeated Frei tests elicited negative results. Cultures for tuberculosis and fungi were negative. A green *Streptococcus*, *Staphylococcus aureus* and *Corynebacterium* were cultured. The patient has had surgical excision of the granulomatous areas.

DISCUSSION

DR HENRY MICHELSON, Minneapolis. I believe that one may consider this entire group of diseases under one general heading and include the dissecting cellulitis of the scalp and acne conglobata. In spite of the fact that they are called pyodermas, they really are conditions involving the subcutaneous tissues much more than the skin. I feel that one must sound a warning about the overuse of roentgen rays. When the patient is first seen, especially with hidradenitis and if the condition is not too severe, a fair trial with roentgen rays is permissible, but roentgen rays should by no means be continued if there is no response and the condition continues to get worse. I have seen patients severely damaged with the continued use of roentgen rays.

DR FRED T. BECKER, Duluth, Minn. In regard to the Negro woman with the vulvar involvement, I will say that from the red beefy appearance of the granulation tissue, which undoubtedly had been disturbed from treatment, I suspected granuloma inguinale. After seeing many of these cases during the past four years in the South, I found that the organisms are particularly difficult to demonstrate. It was the practice of my co-workers and me to scrape the lesions

with a sharp scalpel and smear the scrapings on a slide, using either the Wright or the Giemsa stain, with, however, twice the length of time for the staining technic as is used in blood smears. There is also a tendency in these cases to relapse after treatment, and it usually is advisable to continue stibophen administration three times a week for a period of ten weeks and then continue the injections once a week for at least six months.

DR. ROBERT R. KIERLAND: The similarity between the picture now presented by this patient and that of granuloma inguinale is great. However, this has been due to repeated surgical excision of the granulomatous masses and canalizing abscesses, which leave a velvety granulating base. Complete search for Donovan bodies had been done before her admission and was done here as well, with completely negative results. In addition, before her admission here she had had extensive courses of antimony preparations, including stibophen, and, while here, she had over 15,000,000 units of streptomycin without any benefit whatsoever.

I would like to have Dr. Barton discuss his recent experience in the treatment of granuloma inguinale with streptomycin.

DR. ROBERT L. BARTON, Dubuque, Ia. (by invitation): During the past five months I have treated 3 patients with granuloma inguinale with streptomycin, 20,000 to 30,000 units every three hours intramuscularly over a period of three to five weeks. In 1 of the patients the lesions completely disappeared and did not recur after three months of observation. In the other 2 patients, who were treated for necessarily shorter periods of time inasmuch as our supply of streptomycin was exhausted, the lesions improved rapidly almost to the point of complete healing, but relapsed within a month after the cessation of streptomycin therapy. I was favorably impressed, however, by the response of this disease to streptomycin.

DR. WALTER C. POPP, Rochester, Minn.: Roentgen therapy is of value in hidradenitis suppurativa in perhaps two ways: in the fairly acute phase it does tend to ameliorate activity of the process; secondly, in the chronic phase it sometimes tends to reduce the induration and render the process inactive. Only too often hidradenitis is treated with low voltage roentgen therapy, with about 80 kilovolts and no filtration. Since it is essential to have sufficient penetration to affect a lesion at any depth, it seems reasonable that voltages much higher than 80, perhaps in the range of 130 to 140 kilovolts, with 3 or 4 mm. of aluminum filtration, are much more beneficial. At no time do we treat lesions of this nature with low voltage radiation. The dosage for individual treatments depends largely on whether the process is acute or chronic.

Thromboangitis Obliterans.

O. T., a 37 year old man, unemployed, was essentially in good health until 1942, when multiple small tender nodules appeared on both legs. From 1942 until the present there have been repeated episodes of superficial migratory thrombophlebitis, with lesions appearing on his wrists, arms and legs. He has complained of intermittent claudication in his left leg since 1943 and in his right leg since 1945. In 1944, after treatment for an ingrown toe nail, a painful ulcer developed around the nail, which healed after eleven months of bed rest in an army hospital. The ulcer reappeared on the same site in May 1946 and has been unresponsive to treatment. Since August, after dissection of part of the fourth finger nail of the right hand, an ischemic painful ulcer has been present.

The past history is essentially normal, save that he has smoked a package of cigarets daily from the age of 23 to the time of his admission here.

Physical examination reveals an ischemic ulcer on the lateral surface of the right great toe nail and on the distal tuft of the fourth finger of the right hand. There is a positive Allen sign of the right hand, decided pallor on elevation of both hands and rubor on dependency of both feet. Results of laboratory studies were essentially negative. Roentgen examination of the fourth finger of the right hand shows early destructive changes in the tufts of the distal phalanx. The peripheral pulsations are shown in the table.

Peripheral Pulsations

	Right	Left
Radial	3	3
Ulnar	0*	2
Femoral	4†	4†
Popliteal	4†	3
Posterior tibial	0*	2
Dorsalis pedis	2	0*

* Absent pulse

† Normal pulse

Thromboangitis Obliterans

J. A. H., a 34 year old clerk, was essentially in good health until July 1945, when, after the paring of a callus on the plantar surface of his right great toe, an ulcer developed which has failed to heal and has gradually increased in size and depth. In the last month he has had severe pain in this lesion. His past history is essentially normal, save that he has had cold feet for three years and has smoked at least a package of cigarets a day since the age of 17 until a month ago. There has been no history of migratory thrombophlebitis or of intermittent claudication.

Physical examination revealed an ischemic ulcer on the plantar surface of the right great toe. There is elevation pallor of both feet, dependency rubor and delayed venous filling time of the superficial veins on the dorsa of the feet.

Results of laboratory studies were negative. Roentgen examination of the right great toe showed osteoporosis of the distal phalanx. The peripheral pulsations are shown in the table.

*Peripheral Pulsations**

	Right	Left
Radial	4	4
Ulnar	4	4
Femoral	4	4
Popliteal	4	4
Posterior tibial	0	3
Dorsalis pedis	0	0

* 4 is normal pulse, 0 is absent pulse

DISCUSSION

DR. E. M. FARBER, Rochester, Minn. (by invitation). The simplest operative procedure involving the extremities of patients with unrecognized obliterative peripheral vascular disease is fraught with danger. The removal of a callus from the toe of the last patient reported resulted in the formation of an indolent ischemic ulcer. This case illustrates that Buerger's disease may have an insidious onset, for at the time of the removal of the callus there was no history of migratory

thrombophlebitis, intermittent claudication or rest pain, the pathologic changes may have involved at this time only the vessels of the right great toe. When the patient was examined nine months after the callus had been removed, one had little difficulty in recognizing the presence of thromboangitis obliterans. Physical examination of the lower extremities revealed the presence of rubor on dependency, pallor on elevation and absence of arterial pulsations of the right foot.

The other patient, prior to surgical removal of an ingrown toe nail, had a history of migratory thrombophlebitis and intermittent claudication of several years. Failure to recognize the peripheral vascular insufficiency in this patient resulted in the formation of an ischemic ulcer.

The prognosis for the patient with the ischemic ulcer of the right great toe is better than in the patient with the ischemic ulcers on the toe and finger, but the course in each patient, irrespective of absolute bed rest, the use of antibiotics and so forth, is expectedly slow. Sympathectomy for the lower extremities in patients with Buerger's disease is more effective than sympathectomy for the upper extremities. For that reason, the patient with the ischemic ulcer on the dorsum of the toe will undoubtedly have a shorter hospital course.

Acrosclerosis

Mrs. O. T., a 42 year old married woman, in December 1945 noted swelling of the fingers, with the color changing to a purplish and greenish white when the hands were exposed to cold. There was a "solid" feeling to the forearms in the morning.

The hands, legs and feet are somewhat ivory colored. Pressure on the hands and feet results in pronounced blanching. The skin of the hands and feet is shiny, smooth and slightly sclerosed but not hidebound to the underlying tissues. The face is uninvolved.

Acrosclerosis, Raynaud's Disease with Scleroderma.

Mrs. H. L., a 35 year old married woman, first noted swelling of the hands in January 1946. When the hands became cold, they became blue, then yellow and red when warmed. In February, similar changes were noted in the feet. About two months ago the face became swollen and stiff. Roentgen examination of the hands and knees showed minimal arthritis of the terminal phalangeal joints. Roentgen examination of the teeth showed the characteristic widening of the periodontal space between the posterior teeth on both sides, as originally described in cases of acrosclerosis by Dr. E. C. Stafne. No dental abscesses or pyorrhea was noted.

Acrosclerosis

Mrs. J. P., a 49 year old native of Santiago, Chile, first came to the Mayo Clinic in August 1937, at which time a diagnosis of acrosclerosis was made. At that time the patient had had vasomotor changes of the fingers for about five years, especially on exposure to cold and with emotional disturbances. At the time of her admission there was definite sclerosis of the fingers, with necrotic ulcerations of the finger tips. Some tightening of the skin of the face with narrowing of the lips and a mild degree of sclerodermatous infiltration in the upper part of the chest were noted. Bilateral thoracic sympathetic ganglionectomy and trunk resection were done on August 25.

The patient has been observed and treated at the clinic on six occasions since her original visit but has had a steady downward course. The fingers have become definitely shortened, although the degree of ulceration of the finger tips is minimal.

The patient has had sclerodermatous infiltration of the esophagus, which has responded to esophageal dilatation

She has, in addition, cholecystitis with stones and chronic duodenal ulcer

Acrosclerosis

J A L, a 54 year old farmer, was well until six years ago, when his hands and fingers became blue and ached on exposure to cold. The feet participated in a similar but less intense reaction. The fingers have gradually become increasingly stiff and swollen and the skin smooth and bound down with almost a boardlike consistency. Ulcerations developed on the finger tips and have healed slowly, leaving stellate scars. There is a sensation of stiffness in the skin of the forehead, and the skin cannot be wrinkled. A recalcitrant superficial ulcer has been present over the external malleolus of the right foot for the past three months. There is no cutaneous sclerosis in the lower extremities, but the feet are cyanotic and cold to the touch even at room temperature.

Skin temperature shows a rise of 11 to 18 degrees (F) in the fingers and toes in response to increased room temperature. Roentgen examination of the esophagus shows definite sclerodermatous changes with impaired peristalsis.

Roentgenograms of the dental regions and of the hands are essentially normal. Results of laboratory studies, including blood calcium and phosphorus, were essentially negative. Biopsy of the skin revealed atypical acrosclerosis.

Acrosclerosis

C J, a 34 year old merchant, observed in 1945 that his fingers and feet became white when exposed to cold, but on subsequent warming they became dark purple and were painful. Shortly thereafter, there was noted ulceration of the finger tips of the right hand. The story of swelling of the hands was vague. In January 1946, however, the skin of the fingers, hands, toes and feet began to harden, and there was stiffness in the joints. By the early part of February he was unable to make a fist.

The induration of the skin has progressed to the point where there are, on many of the bony prominences, superficial ulcerations with crusting. The skin on the hands, forearms and feet is tense and tight. The face has an "ironed-out" expression. There is some thinning of the lips. The skin of the face is somewhat pigmented and of a glistening grayish hue.

Roentgenograms of the esophagus showed sclerodermatous infiltration with atonic musculature. Roentgenograms of the thorax showed minimal fibrosis and calcified tuberculosis in the apex of the right lung.

DISCUSSION

DR STEPHAN ROTHMAN: I have difficulty in understanding the concept of acrosclerosis. If it is meant that acrosclerosis always starts with Raynaud-like signs, I would like to state that in the first 2 cases of the group the disease started with swelling which corresponds with the first (edematous) phase of all sclerodermas. "Acrosclerosis" also may start with arthritic pain and bone changes, because it is a generalized connective tissue disease from the beginning. No doubt there are diffuse and circumscribed forms of scleroderma. But if one subtracts the acrosclerotic type from the group of diffuse scleroderma, I wonder what remains in that group. What is "true diffuse scleroderma?" I would like to ask Dr O'Leary to discuss this point and particularly to mention how often one sees diffuse generalized scleroderma which is not acrosclerosis.

DR REUBEN NOMLAND I had the opportunity to see the second patient from the very beginning several months ago. The thing she complained of primarily was swelling, which at first disappeared at night and reappeared during the day but later became more or less constant. It is only in the last several weeks that she has had sclerosis of the hands, arms, feet and legs and elsewhere. At the beginning I thought that she presented an odd type of angioneurotic edema, but when sclerosis of the skin developed I was uncertain about which form of scleroderma she had. I am still uncertain, because it seems to me that at no time did she complain of Raynaud-like symptoms, at least in the beginning, they were minimal if not absent. I hope that the roentgen examination of the tooth sockets will give a clue as to the definite classification of her disease.

DR E. A. HINES, Rochester, Minn (by invitation) It is important to differentiate Raynaud's phenomenon from other types of changes in the color of the skin, such as acrocyanosis and erythema or persistent pallor of the skin. Raynaud's phenomenon should connote intermittent color changes in the skin, and the intermittency is an important part of the condition. Patients who experience Raynaud's phenomenon have periods when the skin color is normal or practically so and the color changes come in episodes, on exposure to cold and sometimes with emotional disturbance. The changes in color often consist of a three phase color change of cyanosis, pallor and redness, but in many instances only one of these color changes occurs, such as pallor on exposure to cold or cyanosis. I consider this also to be Raynaud's phenomenon even though there is only one type of color change, because the paroxysm is produced by arterial spasm and perhaps venous spasm, and different types of changes of color in the skin may be produced, depending on the extent and severity of the spasm. Raynaud's phenomenon may occur in a variety of different conditions and diseases, including Raynaud's disease, and that is one of the reasons why there has been so much confusion in the diagnosis of Raynaud's disease and scleroderma. In obtaining the patient's history, it is always important that one try to determine when the color changes started in relationship to the changes in the skin. This may be difficult to determine particularly because patients with scleroderma who have color changes, since they are spectacular, are more likely to notice them before they notice other changes, such as stiffness of the skin or difficulty in bending joints, and in many cases one cannot determine definitely which came first. Many of the patients with primary acral scleroderma also have Raynaud's phenomenon, and, to add more confusion to the picture, in some patients with long-standing Raynaud's disease scleroderma may develop, but in many it does not.

The results of sympathectomy for scleroderma with Raynaud's phenomena have not been too good because these patients often have organic changes in the skin and subcutaneous tissues which one should not expect a sympathectomy to affect. Dr O'Leary has done more sympathectomies in acrosclerosis and generalized scleroderma than I have and can give you a better evaluation than I can. I know that in Raynaud's disease one can get good results, practically in 100 per cent, in patients who have lumbar sympathectomy for the lower extremities, that is, they get rid of Raynaud's phenomenon and cold feet and may have no further trouble for years. In the upper extremities the results are much less satisfactory. About one third will get a good result from sympathectomy that will persist, two thirds get temporary results which will persist for months or a year or two and then they have the same trouble again. Since this is true in Raynaud's disease without scleroderma, one can see why sympathectomy in the upper extremities cannot be expected to accomplish a great deal in cases of acrosclerosis. Patients with acral scleroderma who have a severe Raynaud's phenomenon and rather mild scleroderma may get some benefit from sympathectomy, and it should be considered. I am

especially interested, from this point of view, in a recent change in the technic of cervicothoracic sympathectomy, a change introduced, I believe, by Dr Goetz of South Africa, in which only the second thoracic ganglion is removed instead of the lower cervical and upper thoracic chain. Dr J G Love, of the Mayo Clinic staff, has done a few of these operations in patients with Raynaud's disease and Buerger's disease with rather good results in the hands. This is a much less extensive operation than cervicothoracic sympathectomy. The patients are usually out of the hospital in three or four days and are not incapacitated for a long period. If this simpler operation works out, there will be something of a less extensive nature to offer the patients who have acrosclerosis and Raynaud's phenomenon of the hands.

DR PAUL A O'LEARY, Rochester, Minn. These 5 patients with varying degrees of Raynaud's phenomenon and scleroderma were shown primarily to illustrate some of the manifestations of this syndrome. Acrosclerosis, I realize, is not a good term, but I have continued to use it in order to separate these patients, at least for the time being, from patients with frank generalized scleroderma. The more we see of patients with this syndrome the more obvious are its dissimilarities to generalized scleroderma. It is unusual to see the disease in male subjects, the 2 male patients offer several unique features, the outstanding one of which is involvement of the lower extremities, which in the adult man is decidedly more pronounced than it is in female subjects. From the morphologic point of view, patients with acrosclerosis do not manifest the yellow, Carnauba wax hue that is so common in the generalized forms of scleroderma. The distribution of the cutaneous sclerosis in this group of patients is typical, starting in the fingers or hands, then involving the forearms, later the face and upper part of the chest and, on occasion, the feet, it is quite distinct from the course of the disease in the patient who has generalized scleroderma and perhaps sclerodactylia. Patients with acrosclerosis show complications or manifestations of the disease which are characteristic of the entity and are not seen in patients with generalized scleroderma. Among these manifestations is involvement of the esophagus, either in the form of sclerodermatous-like infiltrations or shortening of the esophagus, with resulting hiatal hernias. In a few cases cardiospasm is present. Esophageal dilatation usually gives these patients symptomatic relief. Pulmonary fibrosis (scleroderma?) is not uncommon.

Dr E E Stafne, of our dental staff, has recently called attention to the fact that patients with acrosclerosis have characteristic changes demonstrable in dental roentgenograms. These consist of widening of the peridental spaces and occur mostly about the posterior teeth, although occasionally they may, as the roentgenograms showed today, affect all the teeth. After surveying a large number of roentgenograms of patients with generalized scleroderma, Stafne found only 1 who presented this change.

Another distinction that to me is of great importance is that patients with acrosclerosis have labile vasomotor indexes. One of the men shown has a vasomotor index of 18 degrees (F), meaning that on changing from a cold to a hot room the temperature in his fingers was increased up to 10 C. In patients with generalized scleroderma who subsequently have sclerodactylia, vasomotor indexes are usually of narrow range, in the neighborhood of 2 degrees (F). A similar observation has been noted in the study of the capillary loops of the nail beds of patients with cutaneous sclerosis. Patients with acrosclerosis have a capillary loop similar to that of Raynaud's disease, with dilatation, stasis and slowing of the capillary flow. In the patients with generalized scleroderma and sclerodactylia the capillaries are fewer, large and "feathery" and do not show evidence of stasis in the loops.

Although performance of sympathectomy is of material help in patients with Raynaud's disease, the procedure is of no value in patients with acrosclerosis. I think, too, that the frequency with which acrosclerosis clears spontaneously, apparently when the Raynaud phenomenon becomes minimal or disappears, is another striking feature of the disease. The subcutaneous atrophy which is noted, especially in the cases that clear spontaneously, is another of the striking differences between scleroderma and acrosclerosis. The skin returns almost to normal, but the subcutaneous tissues melt out, however, ankylosis of the finger joints frequently remains in this phase of the disease. Acrosclerosis will occasionally produce spontaneous amputations of the fingers, absorption of the distal phalanges is invariably present in the cases of advanced disease in one degree or another. Spontaneous amputations are rare in Raynaud's disease and unfamiliar to me in patients with sclerodactylia as a part of generalized scleroderma.

I regard cutaneous sclerosis as a symptom rather than as an entity and believe that some day different causative agents or mechanisms will be recognized. It is with this thought in mind that I make a distinction between acrosclerosis and generalized scleroderma with the hope that by so doing we may eventually learn something about the cause of cutaneous sclerosis.

Chronic Discoid Lupus Erythematosus?

Miss Y. J., a 27 year old Negro woman, in 1938 noticed fissuring and irritation of the lips followed by thickening and a white glazed appearance of the vermilion borders. Roentgen therapy was ineffective. Subsequent spontaneous involution of the lesions occurred, however, and residual patches of purplish black pigmentation of the lips appeared. In 1943, a pruritic circinate plaque developed on the left hip. This was followed in 1944 by the development of similar plaques on the dorsal surfaces of the hands and the plantar surfaces of the feet. Roentgen therapy again was ineffective. The patient's family history and systemic review were noncontributory.

Examination at the Mayo Clinic in March 1945 showed bilateral symmetric circumscribed scaling violaceous plaques, 3 to 5 cm in diameter, on the dorsolateral surfaces of the hands and on the plantar-medial surfaces of the tarsal areas of the feet. Patchy purplish black pigmented areas were present on the lips, and symmetric telangiectatic mucosal erosions were present on the buccal mucosa opposite the third molars. The results of the general examination were essentially normal except for secondary anemia.

A vitamin A tolerance test showed a rise in the blood vitamin A level to the lower limits of normal. Coincident with the oral administration of 150,000 units of vitamin A daily for eight months, the lesions showed moderate improvement. The anemia responded to treatment with ferrous sulfate.

The patient then received courses of sodium cacodylate, mercury succinimide, typhoid vaccine, bismuth subsalicylate and oxophenarsine hydrochloride without significant improvement in the cutaneous lesions.

In May and June 1946 the lesions on the right and left hands and on the left foot were excised, with skin grafts on the denuded areas. Good surgical results were obtained but subsequently there was recurrence at the edges of the lesions.

The diagnosis from pathologic study of tissue removed from the buccal mucosa was benign leukoplakia. Tissue removed from the hands and feet suggested parakeratosis of Minelli at first and lupus erythematosus or lichen planus later.

Subacute Disseminated Lupus Erythematosus; Alopecia Totalis

B. K., a 27 year old white man noticed the onset of a generalized eruption in August 1944. In November crusted pustular lesions occurred on his scalp and

resulted in the complete loss of hair from the scalp and partial loss of hair from the bearded areas. Loss of axillary and pubic hair occurred without other gross cutaneous changes in these areas.

Examination at the Mayo Clinic in November 1945 revealed almost complete alopecia, scaling, diffuse atrophy and violaceous discoloration of the scalp, cheeks and forehead and bilateral, symmetric, keratotic follicular plugging on the knees and on the elbows. Fungi could not be demonstrated in the lesions. The diagnosis from histologic study of tissue removed from the left cheek was subacute disseminated lupus erythematosus.

DISCUSSION

DR CARL LAYMON In my opinion this man presents a combination of alopecia totalis and superficial lupus erythematosus of the face which is now inactive. I think that cicatricial alopecias, such as pseudopelade and folliculitis decalvans, can be ruled out, since neither of these diseases causes a total loss of hair on the scalp. I could not see evidence of lupus erythematosus of the scalp.

DR FRANCIS LYFCH The causes of lupus erythematosus are not yet known, but endocrine disturbance has been observed frequently and many regard it as a factor in the course of this disease. Lupus erythematosus is less common in men than in women, in this man there is evidence of endocrine abnormality, as shown by the body build and the feminine distribution of adipose tissue as well as the alopecia.

A Case for Diagnosis (Tuberculid?)

A B, an 18 year old Negro girl, has had a generalized pruritic papular and vesicular eruption with involvement of the mouth for the past two years. This has been accompanied with an inflammatory condition of the eyes and by migratory polyarthritides. She gives a history of hospitalization elsewhere from November 1942 to March 1943, because of possible pulmonary tuberculosis.

Physical examination reveals a generalized papular and vesicular eruption of the skin with crusted excoriations, scars and pigmentation, accompanied with erosions on the mucous membrane and an anal fissure, swelling and entropion of the eyelids with injection, bulla formation, superficial ulceration, scarring and cicatricial contraction of the conjunctivas, painless swelling of the right knee, and localized left hydropneumothorax with fibrous tuberculosis of the apex of the left lung. Results of serologic tests for syphilis were negative. The result of a tuberculin test (purified protein derivative, first strength) was strongly positive (Microscopic sections were presented).

DISCUSSION

DR JOHN MADDEN, St Paul I thought that there was a possibility that the patient had dermatitis herpetiformis. The lesions were in the areas that ordinarily are involved. The eruption was itchy, many of the lesions were vesicular, and the microscopic section showed vesicles with a high percentage of eosinophils in the infiltrate.

Erythema Induratum

Mrs I W B, a 53 year old white housewife, noted nine months ago a pigeon-egg-sized, nontender deep-seated nodule in the right calf. The overlying skin was attached to the lesion and subsequently became violaceous, thickened and scaly. Three months ago four roentgen treatments, given this area by her family physician, were without benefit. One month ago ulceration and purulent discharge developed.

in the area. The left calf became involved seven or eight months ago with small deep-seated nodules, which have gradually enlarged and coalesced but have shown no further progression to date.

The patient is otherwise asymptomatic and has no history of tuberculosis. A roentgenogram of the thorax does not show tuberculosis, but the reaction to the tuberculin test (purified protein derivative, single strength) is strongly positive. The sedimentation rate is 18 mm per hour. A biopsy specimen taken elsewhere two months after onset was reported as showing chronic granuloma, possibly of tuberculous origin, the histologic picture as recently reviewed here is consistent with erythema induratum. A mild degree of lichen simplex chronicus is present on the extensor aspect of the forearms.

DISCUSSION

DR LOUIS A. BRUNSTING. Erythema induratum usually occurs on the legs of women who are much younger than this patient. In the early stages the diagnosis is difficult and biopsy of an early nodule may reveal pathologic changes which are nonspecific in character, resembling those of so-called nodular vasculitis.

As regards treatment, it is necessary not only to consider the general health of the patient but also to control the edema of the legs, and this is best done by the application of spiral bandages of Para rubber.

DR HENRY MICHELSON. My co-workers and I have treated a small number of patients with the Charpy vitamin D₂ treatment and there has been enough improvement to make us believe that this treatment is worth while. We have also used this treatment in lupus vulgaris, and, although the results have not been as startling as reported in France and England, the treatment is worthy of trial in all such conditions.

Lupus Vulgaris

M. P., a 64 year old married woman, noted the first lesion on her forehead two and a half years ago, followed in six months by the appearance of other lesions of the cheeks, nose and ears. She has ten discrete patches, varying in size up to 5 cm. The large plaque is pigmented and scaling, with atrophic center, and under diascopic pressure shows numerous apple-jelly nodules throughout. Histologic examination revealed lupus vulgaris. A roentgenogram of the thorax showed a dilatation of the aorta but is otherwise normal. The tuberculin reaction (purified protein derivative, single strength) was positive (2 plus). The sedimentation rate was 48 mm per hour. Results of serologic tests for syphilis were negative. Roentgenograms of both hands and fingers showed minimal hypertrophic changes of the phalangeal joints, which the roentgenologists said were not compatible with the diagnosis of sarcoid.

The patient is presented because she is at present receiving streptomycin for lupus vulgaris. She has had only five days of treatment and, of course, has not yet shown any significant changes.

DISCUSSION

DR HENRY MICHELSON. This patient presents difficulty in diagnosis, both clinically and microscopically. I would consider lupus vulgaris, lupus erythematosus, especially of the LeLoir type, and sarcoid. I did not believe it to be lupus vulgaris because the lesions were so numerous and there was so much destructive scarring without any visible lupus nodules. I do not believe that the microscopic observations were conclusive. The diagnosis might be any of the aforementioned conditions and still be consistent with the microscopic picture.

DR PAUL A O'LEARY The exhibit of lantern slides showing the effects of streptomycin in patients with various types of cutaneous tuberculosis was probably not seen by all of you Accordingly, a few comments in regard to our experience with this antibiotic might be of interest Streptomycin has been difficult to obtain, and in our early experience some of it was impure, so that with a limited amount of the drug, an uncertain supply, some impurities and no precedence, we found it necessary to "feel our way along" Streptomycin was originally given in the same manner as penicillin, namely, intramuscularly at three hour intervals, with doses of 20,000 units or more We learned some time ago that streptomycin in small doses, that is of less than 500,000 units a day, is not of value in patients with cutaneous tuberculosis, but as the doses were increased we were encouraged by the better results Now patients are given approximately 2,000,000 units, or 2 Gm, a day, 1,000,000 units of streptomycin is equivalent to 1 Gm It is given while the patient is ambulatory, at the rate of two injections a day, 1 Gm in the morning and 1 Gm in the evening, intramuscularly, preferably in the buttocks

The complications from streptomycin therapy are similar to those that are noted from penicillin, in addition, however, vertigo develops in some patients who receive large doses, which, unfortunately, in a few patients has persisted now for many months following the cessation of the use of streptomycin The patients with scrofuloderma and secondary mixed infection have thrived best, the ulcerations have healed and tend to remain healed One woman with the ulcerated form of lupus vulgaris failed to derive any benefit from promizole® (4, 2'-diaminodiphenyl-5'-thiazole sulfone) or diasone® (disodium-formaldehyde-sulfoxylate-diaminodiphenyl-sulfone), but, as noted from the slides, derived striking benefit from streptomycin We were dismayed, however, that a biopsy specimen taken the day the patient left for home, after she had received 120 Gm of streptomycin, still showed active tubercles, even though the ulceration was entirely healed

We do not feel at the moment that streptomycin is by any means the last word in the treatment of cutaneous tuberculosis, although we have noted a sufficient amount of encouragement in certain patients with cutaneous tuberculosis to continue to give the antibiotic a more extended trial

Ragweed Dermatitis

E F, a 34 year old farmer from Western Canada, for the past three years has had a recurrent eruption of the face, neck, arms and legs appearing each June and persisting until the first frost In winter he is much improved, there being only residual lichenification of the flexures of the elbows and popliteal areas There is no personal or familial allergic history except that one sister has had eczema His wife is said to have a similar condition Patch tests elicit strongly positive reactions to small and western ragweed

DISCUSSION

DR STEPHAN ROTHMAN It is a remarkable fact that pollen eczema is the only eczematous contact dermatitis which simulates neurodermatitis so closely that differentiation on the basis of the clinical picture is practically impossible I wonder how this could be explained

DR HENRY MICHELSON In my experience, this condition does not subside with the occurrence of frost or with the advent of winter That is the point that confuses us so much, although we realize that the patients may continue to get specific irritation from various things with which a farmer comes in contact It

seems to me the ragweed irritant establishes a condition which is hardly distinguishable from atopic eczema

DR. CARL LAYMON Dr Michelson mentioned that many cases of ragweed dermatitis persist well into winter, long after frost Ragweed dermatitis occurs most frequently in farmers, even after frost these persons still come in contact with ragweed which is contained in hay which they feed their stock It has also been noted many times that the longer the patient has ragweed dermatitis the greater is the tendency for the disease to become perennial

DR. JOHN MADDEN Recently I have seen 3 cases in which the disease looked like acute contact dermatitis following ragweed injections for hay fever These eruptions did not occur in the usual sites of ragweed dermatitis One was on the sides of the face, one on the extensor surfaces of the forearms and another on the sides of the neck The eruptions recurred after each injection until the dose was reduced Whenever patients who are receiving injections for any allergic disease have an eruption, the injection should always be thought of as the cause

DR. REUBEN NOMLAND I would like to call to Dr Michelson's attention that grinding of small grains, wheat and oats but not corn, is apt to result in an attack of dermatitis in persons sensitive to short ragweed The allergen is present on the small grain, but not on corn, which is protected by the husk In the treatment of sensitivity to short ragweed, I think that I have had moderate success in desensitization by giving increasing doses of an extract The entire dry plant is extracted with ether, and the resultant oily extract is dissolved in a vegetable oil and given orally in a capsule in increasing doses I have recently spoken to two dermatologists who felt that they could desensitize their patients, one by giving the powdered leaves enclosed in a capsule and the other by giving increasing doses of a ragweed tea made from the entire plant Ragweed dermatitis shows many of the involved areas similar to those of atopic eczema, but involvement of the genitalia and especially of the eyelids is characteristic of ragweed sensitivity I routinely make patch tests with many weed extracts and rarely do I find that giant ragweed causes dermatitis

DR. ROBERT L BARTON (by invitation) As Dr Lynch and Dr Rothman pointed out, the similarity between ragweed dermatitis and atopic eczema is sometimes confusing In this connection it is worth while to recall that, whereas in atopic dermatitis white dermographism is the rule, in ragweed dermatitis red dermographism is commonly elicited This patient revealed a red dermographism when stroked on the face

DR LOUIS A BRUNSTING Atopic dermatitis and contact sensitivity to ragweed are often combined in the same patient I have never seen an instance in which treatment by desensitization changed the reaction to the patch test to negative, although there may be some degree of hyposensitization so that a measure of relief from the periodic recurrence is obtained, this is helped too, as the patient learns what situations in his environment he should avoid

Harry A. Cumming, M D, *President*

Rodney F Kendall, M D, *Secretary*

Jan 24, 1947

Mycosis Fungoides, Plaque Type Presented by DR S E SWEITZER, Minneapolis

A Case for Diagnosis (Lymphoblastoma?) Presented by DR S E SWEITZER

Xanthoma Tuberosum with Lesions on Palms and Elbows Presented by DR S E SWEITZER

Benign Pemphigus Presented by DR FRANCIS W LYNCH, St Paul

Extensive Morphea Presented by DR CARL W LAYMON

Argyria Uninfluenced by 2,3-Dimercaptopropanol (Bal) Presented by DR H E MICHELSON

A Case for Diagnosis (Lymphedema of the Lower Part of the Leg) Presented by DR S E SWEITZER

J H, a male infant aged 6½ months, was noted to have at birth enlargement of the lower part of the left leg, not including the foot. One week after birth, roentgen examination of the leg was thought to reveal a fracture. A cast was applied and left on for about four weeks. The patient was first seen on Oct 1, 1946, at which time the lower part of the leg measured 1 inch (2.5 cm) greater in circumference than the right leg. There was no pitting of the leg on pressure although it did show some dimpling, and the process resembled subcutaneous fat necrosis. Two biopsies were reported as showing no pathologic changes.

Examination reveals uniform enlargement of the lower region of the left leg. The general health is good, and the baby's weight is now about 25 pounds (11.3 Kg).

Roentgen examination of both legs on Oct 10, 1946, was reported as follows: "There is marked swelling or hypertrophy of the soft tissue of the left leg, including the muscle, which is uniform in density. The shaft of the left tibia is approximately 0.5 cm longer than the right, and the cortex of the left tibia and fibula is thicker than on the normal side, with an increase in the anterior bowing of the left tibia. The findings are consistent with diffuse lipomatosis of the soft tissue of the left leg as well as hemangioma and are not characteristic, as far as we can determine, of any one particular pathologic condition. The hypertrophy of the bones is apparently associated with the soft tissue changes."

DISCUSSION

DR EUGENE FARBER, Rochester, Minn (by invitation) I think that the possibility of congenital arteriovenous fistula should be considered. Any infant who has one leg or lower extremity larger than the other, especially with an increase in the size of the bones, makes one think of this. I could not hear a murmur in the upper part of the thigh, however, nor could I feel an area of increased temperature. In congenital lesions of this sort, there may be multiple angiomas. There was no pitting on pressure. It was my impression that this unilateral swelling might be secondary to some congenital disorder in the arteries or veins of this extremity.

DR SAMUEL E SWEITZER, Minneapolis The leg varies in size. If an arterial factor were present, it could stay the same size. Now it is a bit bigger than the last time.

DR HARRY A CUMMING, Minneapolis It would be interesting to know what the surgeon who performed the biopsy found at the operation. When I did a punch biopsy, a considerable amount of lymph drained out.

Nevoxanthoendothelioma (Numerous Tumors on the Scalp and Trunk)

Presented by DR S E SWEITZER

C P, a male infant aged 6 months, presented a yellowish tumor 15 cm in diameter located on the right cheek shortly after birth. At 2½ months, another tumor appeared on the front of the scalp. Since then numerous small painless nodules have developed over the scalp and then on the body. The child was otherwise normal. It was born six weeks prematurely by a cesarean section.

Examination reveals firm, painless, yellowish nodules scattered on the scalp, face and body. The largest lesion on the right cheek, approximately 2.5 cm in diameter, shows central depression from excoriating. There is also a large swelling over the right eyebrow covered by normal skin. Roentgenograms of this lesion show no bony involvement.

The histologic section confirms the clinical diagnosis.

DISCUSSION

DR CARL W LAYMON, Minneapolis: There are several interesting features about this case. It is the most extensive one that I have ever seen. In most cases of nevoxanthoendothelioma there are one or two groups of papules and nodules located at the extensor surface of the extremities. In this case there are dozens of lesions distributed diffusely over the head, trunk and extremities. In most cases of nevoxanthoendothelioma there is hyperlipemia and in most of those which have been reported there has been spontaneous involution by the time the patient was 2 years old. I feel that the prognosis in the case is good despite the large number of lesions.

DR FRANCIS W LYNCH, St Paul: About twelve years ago Dr Bell examined sections from the case which I presented before the Mississippi Valley Conference. It was his impression that, rather than a xanthomatous process, we were dealing with a nevoid process with degeneration of the nevoid cells.

DR CARL W LAYMON, Minneapolis: The consensus among dermatopathologists is that nevoxanthoendothelioma presents a distinctive histopathologic picture characterized by the presence of xanthomatous cells plus endothelial and Touton giant cells.

Basal Squamous Cell Epithelioma of the Back

Presented by DR S E SWEITZER

Squamous Cell Epithelioma of the Vulva in a Woman Aged 73 Years

Presented by DR S E SWEITZER

Wooly Hair Nevus

Presented by DR S E SWEITZER

M P, a female child aged 4, of Italian extraction, was apparently normal at birth and had a normal growth of slightly curly hair. At the age of 5½ months all the hair was shed and replaced by a scanty down. Since there was no growth of hair by the time the child was 2 years old the mother had the child's head shaved several times on the advice of friends.

Examination reveals scanty growth of hair with a fine kinky texture. There are no signs of any inflammation of the scalp.

DISCUSSION

DR E T CEDER, Minneapolis: I wonder if some observers might object to the term "nevus" as applied in this case. Fred Wise (*Medical Journal and Record*

125 545, 1927) reported some cases of wooly hair nevus which were characterized by localized areas of wooly hair among normal hair. In this case it is a generalized affair. There is some suggestion of ectodermal defect in the quality of the hair, but the child presents no other evidence of such defects.

Keloid of the Chin Presented by DR S E SWFITZER

A Case for Diagnosis (Ulcer on the Ankle) Presented by DR S E SWEITZER

W J, a man aged 20, was previously shown at a meeting of the Minnesota Dermatologic Society in 1941 with ichthyosis. He was admitted to the Minneapolis General Hospital Surgical Service on July 1, 1946, because of a large ulcer on the medial aspect of the left ankle together with bilateral inguinal adenopathy and multiple small draining sinuses in both inguinal regions. The patient stated that about eight weeks prior to his admission a small papule developed over the internal malleolus of the left ankle. This became infected and resulted in an ulcer which progressively increased in size in spite of local treatment. After a period of six weeks he noticed drainage from the inguinal region. His past history revealed that he had been treated seven years previously with a body cast for kyphosis and scoliosis of undetermined cause. While in the hospital he was treated with various types of antiseptic soaks and packs, bed rest and elevation of the leg. He was also given 25,000 units of penicillin every three hours for a total of 2,500,000 units. During the first three weeks of hospitalization he had a temperature from 99 to 100 F. The ulcer of the leg gradually healed, and he was discharged from the hospital on September 28 completely asymptomatic.

Examination now reveals a raised bluish red area on the medial aspect of the left ankle about 7 cm in diameter, with a small central ulcer. There are also several small granulomatous sinuses in both groins which are draining a small amount of seropurulent material.

The hemoglobin content was 83 to 88 per cent, the erythrocytes numbered 4,370,000 and the leukocytes numbered 6,200 to 10,800, with a normal differential count. Tests for syphilis gave negative reactions. The blood cholesterol was 150 mg and the blood plasma protein 6.8 Gm per hundred cubic centimeters. The sedimentation rate on admission was 83 mm in 60 minutes and on discharge 16 mm. Cultures of the ulcer on the leg and drainage from the inguinal sinuses revealed *Staphylococcus albus* and *Staph aureus*, diphtheroids and gram-positive cocci. One smear of material from a lesion in the groin was reported as showing acid-fast bacilli in addition to gram-negative and gram-positive cocci, spirochetes and fusiform bacilli and diphtheroids. The sputum did not contain tubercle bacilli. Guinea pig inoculation of material from the ankle resulted in negative reactions after eight weeks. Mantoux and Frei tests gave negative reactions. Agglutination tests for *Brucella melitensis* and *Pasteurella tularensis* elicited negative reactions. Roentgenograms of the spine revealed kyphosis with moderate hypertrophic changes, and roentgenograms of the left ankle were normal.

Histologic sections were shown.

DISCUSSION

DR JOHN F MADDEN, St Paul. The lesions on the patient's chest, groin and back are those of acne conglobata. The lesion on the leg could well have been a secondarily infected traumatic ulcer. I think that these lesions are all part of a general pyogenic infection.

DR HARRY A CUMMING, Minneapolis There is little question that the lesions on the chest are those of acne conglobata I must confess that I did not see them until this evening The patient also presents ichthyosis of the follicular type, for which he was presented previously

DR F T BECKER, Duluth, Minn In military personnel whom we observed in hot, humid climates extensive acne lesions developed These became generalized and occasionally involved the legs and arms I believe that this patient has a deep, cystic type of acne, and treatment should be directed toward eradication of these cysts My experience with penicillin in this type of case was that it was not too beneficial but it did clear up the secondary infection

DR E T CEDER, Minneapolis I should like to relate the sequence of events Originally the patient had a large granulomatous ulcer of the leg There was adenitis, with no suppuration and no sinus formation After a period of about a month, the sinus developed in the left inguinal area He had no lesions elsewhere

DR E DELAMATER, Rochester, Minn (by invitation) I palpated the area around the lesion, and I thought that there were several loculations of fluid material I wonder whether the aspiration of some pus, which perhaps would not be contaminated by the ulcer itself, might indicate some organisms such as those of actinomyces

The bones are not involved in the roentgenograms Proper culture technique might be indicative even though sulfur granules are not present Roentgen therapy given to the lesion, followed by culture from five to ten days later, might show the granules which form in the suppuration

Erythema Induratum Presented by DR CARL W LAMON

Heberden's Nodes with Cysts on the Fingers Presented by DR S E SWEITZER

DISCUSSION

DR E T CEDER, Minneapolis I provoked the presentation of this case because of the problem of differentiating the cysts associated with Heberden's nodes from synovial cysts Synovial cysts have a synovial lining In Heberden's node cysts there is not supposed to be any synovial proliferation The cystic degeneration is merely a soft tissue or bursal reaction

DR JOHN F MADDEN, St Paul I agree in the main with Dr Ceder's differential diagnosis between Heberden's nodes and synovial cysts However, synovial cysts may be multiple although they usually are not In either instance the most important thing is not to attempt their removal by surgical means If an attempt is made to remove synovial cysts surgically, varying degrees of infection and ankylosis of the joint often follow

A Case for Diagnosis (Stasis Dermatitis?) Presented by DR S E SWEITZER

J W, a man aged 64, stated that he had had varicose veins for the past twenty-five years He had worn elastic bandages off and on during the past twenty years because of intermittent swelling with redness of the legs He had had no other treatment for his veins and no previous ulceration of the legs On Dec 18, 1946, an acute, vesicular, pruritic contact dermatitis of the hands and forearms developed after contact with boiler compound He was treated with wet dressings and ointments, with improvement Nine days ago ulcerations of the lower extremities developed Examination reveals multiple hemorrhagic

ulcerations involving the lower part of both legs, more marked on the left. There is also a diffuse pigmentation of both legs. The ulcers are covered with dark crusts. The blood pressure is 134 systolic and 76 diastolic.

DISCUSSION

DR E. T. CEDER, Minneapolis: I thought this case was of interest because of the nature of the ulcerations. They appeared suddenly, in one crop on both legs, as small infarcted areas surrounded by a zone of purpura. There was evidence of stasis present, as manifested by edema, and varicosities. These lesions all developed in a period of two or three days and are exquisitely painful. They did not impress me as being typical of stasis dermatitis or stasis ulceration, and I wonder what the opinion of some of the other observers might be.

DR EUGENE FARBER, Rochester, Minn. (by invitation): This patient has obvious chronic venous insufficiency. However, I had him stand erect and observed that almost none of the lesions are located directly over an incompetent vein. All are on the anterior surface of the legs and are readily within reach.

This patient has a normal blood pressure for his age. The leg ulcers in hypertensive patients, which we recognize are not generalized but are one or two in number, occur more frequently around the lateral surface of the ankle and are ischemic. They do not respond to any form of local therapy but seem to follow an uneventful course, sometimes taking six to eight months before healing. When an ischemic-appearing ulcer develops on the leg or ankle of a patient with hypertensive vascular disease and there is no evidence of chronic venous insufficiency or thromboangitis obliterans, an ischemic ulcer due to arteriolar sclerosis should be considered.

I cannot think of any ulcerative disease of the legs with which this could be classified. I think this ulcerative process should be considered as factitial or self-induced.

Neurofibromatosis (Von Recklinghausen's Disease) Presented by DR S. E. SWEITZER

Acrodermatitis Chronica Atrophicans with Ulceration Presented by DR S. E. SWEITZER

Rheumatic Nodules Presented by DR S. E. SWEITZER

P. S., a white man aged 54, stated that he first noted subcutaneous nodules in the tips of his thumbs and on both elbows and heels about fourteen years previously after an attack which was diagnosed as acute rheumatic fever. These nodules were not tender or painful. Large nodules on the elbows and heels were excised in July 1946.

Examination reveals four firm subcutaneous nodules on the palmar aspects of both thumbs. They are not tender. The elbows and heels show healed post-operative scars.

Roentgenograms of the hands reveal hypertrophic changes of the interphalangeal joints of both thumbs with no evidence of soft tissue tumor or calcification.

Parapsoriasis en Plaques (Brocq) Presented by DR S. E. SWEITZER

Chronic Dermatitis Resembling Mycosis Fungoides Presented by DR S. E. SWEITZER

NEW ENGLAND DERMATOLOGICAL SOCIETY

Bernard Appel, M D , *President*

G Marshall Crawford, M D , *Secretary*

April 10, 1946

A Case for Diagnosis (Tuberculosis Due to Inoculation?) Presented by
DR JOHN G DOWNING, Boston

A Case for Diagnosis (Psoriasis? Parapsoriasis? Neurodermatitis Dis-
seminata?) Presented by DR JOHN G DOWNING, Boston

A Case for Diagnosis (Granuloma Annulare of the Hand? Porokera-
tosis?) Presented by DR. S J MESSINA, Boston

Fox-Fordyce Disease Presented by DR BERNARD APPEL, Lynn, Mass

A Case for Diagnosis (Dermatitis Factitia?) Presented by DR F RONCHESE,
Providence, R I

Tuberculosis Colliquativa (Scrofuloderma) Presented by DR BERNARD
APPEL, Lynn, Mass

Mycosis Fungoides Presented by DR M M TOLMAN, Boston

Papulopustular Dermatitis Medicamentosa (Sulfasuxidine) Presented by
DR C GUY LANE, Boston

Lymphosarcoma of the Skin Presented by DR FRANCIS M THURMON, Boston

Sarcoidosis of the Skin Presented by DR ALFRED HOLLANDER, Springfield,
Mass

Generalized Scleroderma Presented by DR. FRANCIS M THURMON, Boston

Bernard Appel, M D , *President*

G Marshall Crawford, M D , *Secretary*

Oct 9, 1946

Dermatitis Factitia Presented by DR. C GUY LANE, Boston

Hemangioma Presented by DR W J MACDONALD, Boston

Lichen Planus (Hypertrophic Type with Bullae); Psoriasis Presented by
DR G MARSHALL CRAWFORD, Boston

Moniliasis of Mouth, Larynx, One Finger and Vagina Presented by DR.
J H SWARTZ, Boston

An 11 year old white girl, E F, is presented with mucocutaneous lesions of
four years' duration. The first complaint was soreness in the mouth, and white
patches were discovered on the buccal mucosa. Shortly afterward swelling and

tenderness developed in the terminal phalanx of the left middle finger. At some unknown later date, the patient experienced vaginal pruritus with lesions similar to those in her mouth. There have been partial remissions and exacerbations of symptoms at irregular intervals.

This little girl's mouth exhibits lesions involving the buccal mucosa and various portions of the tongue. These consist of sharply defined, whitish, firmly adherent membranes. There is fissuring at both oral commissures, with a slightly glazed appearance. The labia minora exhibit whitish patches similar to those in the mouth. The terminal phalanx of the left middle finger is slightly swollen. There is thickening of the finger nail, with distortion and opacity of the nail plate.

This patient spent several months in the Massachusetts General Hospital. Laryngoscopy showed the same whitish membranous patches in the larynx. Microscopic examination of scrapings from the mouth, vagina and finger nail revealed sporelike bodies suggestive of monilial organisms. The same material planted on Sabouraud's mediums produced colonies identified as *Monilia albicans*. Results of roentgenologic examination of the chest were normal. An intradermal test with oidiomycin (1:1,000) resulted in a positive reaction (1 plus). Treatment consisted of general supportive measures, such as high vitamin-high caloric diet and several small transfusions of whole blood. Daily inhalations of ethyl iodide were administered for six weeks. Local applications included streptomycin, 20 per cent sodium caprylate solution, propionic acid-sodium propionate solution and quaternary ammonium compound. The progress of the disease has continued uninfluenced by any of this treatment.

Moniliasis of the Mouth Presented by DR I. H. SWARTZ, Boston

An 18 year old white girl, S. B., occupied as a hairdresser, is presented with oral lesions of six months' duration. The patient first noticed enlarged glands in her neck and shortly afterward found white patches in her mouth. These were asymptomatic at first but spread gradually, and there was subsequently some pain on swallowing.

Examination reveals lesions scattered over the palate and anterior tonsillar pillars. They consist of small grayish deposits which create a mottled appearance on the affected areas. This exudate can be easily removed by scraping revealing a normal-looking mucous membrane. Those on the tonsillar pillars and a few on the soft palate are more whitish.

This patient spent about a month in the Massachusetts General Hospital. It was found that the removal of all exudate was followed by its rapid reappearance in almost identical fashion. Material obtained from the lesions of the mouth grew organisms identified as *Monilia albicans* when cultured on Sabouraud's mediums. Treatment consisted of the application of Gram's solution and subsequently of 20 per cent sodium caprylate solution in each instance after removal of exudate. The disease proved refractory to treatment.

DISCUSSION OF THE TWO PRECEDING CASES

DR. GEORGE E. MORRIS: I would suggest the use of a paint containing 10 per cent methylvrosamine chloride and 10 per cent formaldehyde, to be applied daily.

DR. FRANCIS M. THURMON: There is a solution which I have been evaluating clinically—glycerite of hydrogen peroxide. In the presence of serum and blood cells it liberates oxygen and because of the surface tension of the glycerine it contains, the liberated oxygen is confined to the solution over prolonged periods of time, for twenty-four to thirty-six hours. I have not used the solution in moniliasis. I do know that certain spore-bearing organisms are killed by

oxygenation from this compound. When used as a diluent or for topical applications, it offers a distinct method of therapy. The solution is now commercially available.

A Case for Diagnosis (Bacterid?) Presented by DR M M TOLMAN, Boston, and COMDR W C MARSH, United States Navy Medical Corps (by invitation)

T B B, a 47 year old white American naval captain, is presented with an eruption of over four years' duration. His cutaneous disturbance was generalized but primarily affected the palms and soles. It began soon after a cholecystectomy in 1942, which was complicated by the spilling of bile into the abdominal cavity. Eight grams of sulfanilamide were dusted into the abdomen. The postoperative course was stormy. A month later a severe respiratory infection developed, which was treated with sulfathiazole, treatment with this drug had to be discontinued because of a reaction of undefined type. Shortly thereafter a generalized dermatitis developed, accompanied with enlargement of the liver and spleen, ascites and a systolic murmur heard at the apex of the heart. At that time, examination of the white cells of the blood revealed 60,800 leukocytes per cubic millimeter, with 77 per cent eosinophilia. Biopsy of muscle was performed and a histologic diagnosis of periarteritis nodosa was rendered. By midsummer of 1943 the patient had become relatively asymptomatic and remained so until February 1945. At that time his eruption reappeared, accompanied with the same systemic symptoms. The dermatitis now involved mainly the hands and feet, and since then (twenty months) it has recurred approximately every sixteen days. An intensive search for foci of infection has been unproductive. Many diagnoses have been suggested by the various physicians who have studied the patient, including rheumatic fever, periarteritis nodosa, dermatitis herpetiformis, pemphigus vulgaris and recurrent pustular bacterid.

Examination reveals an eruption mainly on the palms and soles. It consists of vesicles, hemorrhagic vesicles, vesicopustules and pustules. These lesions are surrounded by a zone of erythema and are from 1 to 30 mm in diameter. They are profuse on the palms and soles, but a few are also present on the dorsal surfaces of the hands and feet, on the forearms and in the inguinal regions. The remainder of the integument reveals only an occasional lesion, except on the face and scalp. The hard palate is covered with a yellowish adherent membrane. Three small nonerythematous papules may be seen on the left buccal mucous membrane.

Electrocardiographic tracings were normal. Results of several tuberculin tests were negative, and the reaction to an intradermal test for trichinosis was negative. Repeated examination of the urine gave normal results. The red cells of the blood were normal in number and appearance. Recent examinations of the white cells of the blood have revealed from 9,700 to 60,000 leukocytes per cubic millimeter with 16 to 77 per cent eosinophils. The chloride content of the blood was 316 mg per hundred cubic centimeters. The total protein content of the blood serum was 3.54 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 2.4. The cholesterol and calcium content of the blood were normal. No ova, parasites or abnormal bacteria were found in the feces. Cultures inoculated with material removed from vesicles grew hemolytic *Staphylococcus aureus*, hemolytic *Streptococcus* and nonhemolytic *Staph aureus*.

Treatment has consisted of numerous courses of penicillin, bismuth compound injections, both autogenous and stock vaccines, liver injections, intravenous administration of oxophenarsine hydrochloride, roentgen therapy to the hands and feet (350 r), nonspecific protein given parenterally and injections to block

the stellate ganglions. A great multiplicity of local applications have also been employed. None of these measures have altered the cyclic course of this man's disease.

DISCUSSION

DR. C. GUY LANE. I examined this man with some interest, and I wonder whether the disease belongs to the type which is called "infectious eczematoid dermatitis." I do not know what other name to give to these lesions. The dermatitis began on the hands and feet and has become generalized. I believe that the condition is related to a lowered resistance, a lowered immunity to one of the organisms which reside on or in the skin. No one knows why this occurs in some persons. It would seem that some means of raising this resistance would be a logical method of treatment. I assume that he has had sufficient treatment with sulfonamide drugs and perhaps vaccine as well. If not, I suggest that an attempt be made with autogenous vaccine therapy.

DR. F. RONCHESE. I would use copper iontophoresis (or alibour water). I have employed that solution in 300 or more cases. About 50 per cent of the most recalcitrant conditions responded well.

COMDR. W. C. MARSH. He has had both autogenous vaccines and copper iontophoresis without response.

DR. FRANCIS M. THURMON. I would suggest the diagnosis of periarthritis nodosa.

DR. BERNARD APPEL. Has Wright's opsonic index been determined?

COMDR. W. C. MARSH. It is not in his record to date.

DR. GEORGE E. MORRIS. Has fever therapy been tried?

COMDR. W. C. MARSH (by invitation). We are giving him a course of nonspecific protein injections, using a milk protein product. The internists have advised against typhoid vaccine hyperpyrexia in this case because of possible harm to cardiac and arterial structures, and we are therefore using a milder nonspecific protein therapy.

DR. E. MYLES STANDISH. Is that the reason the tonsils have not been removed?

COMDR. W. C. MARSH. Sin rhinologynologists have agreed that tonsillectomy is unnecessary.

DR. MAURICE J. STRAUSS. There must be something that has not been done. You might consider iontophoresis with formaldehyde.

DR. M. M. TILMAN. This man was exhibited before another dermatologic society, and the diagnosis of periarthritis nodosa was seriously considered. His attacks have been predicted on numerous occasions. An unusual feature of the case is that new attacks occur in exact periodic cycles, and the patient can tell just what will occur next. Each episode begins with pain and continues through the various stages to exfoliation, then, on the eighteenth day, it recurs regardless of all efforts.

DR. BERNARD APPEL. I asked this intelligent patient what he found most helpful from his own personal experience. He got the best results from neoarsphenamine, better than with oxophenarsine hydrochloride.

DR. GEORGE E. MORRIS. Is this man perfectly happy in the Navy?

COMDR. W. C. MARSH. He is now in retirement, so that his mental attitude has nothing to do with it.

DR M M TOLMAN What do the members think of the diagnosis of periarthritis nodosa? This has been confirmed by three pathologists

DR WALLER F LERER It seems reasonable that the patient has periarthritis nodosa From the past history, however, the earlier lesions do not suggest it I think that this is a phenomenon of sensitization, and periarthritis nodosa is a state of sensitization The present cutaneous lesions are compatible with that diagnosis

Angioma Serpiginosum (Schamberg's Disease?) Presented by DR WALTER F LEVER, Boston

Senile Atrophy of the Skin Avitaminosis, Multiple Presented by DR C GUY LANE, Boston

Nodular Nonsuppurative Panniculitis of the Extremities Presented by DR S J MESSINA, Boston

Mrs S H is a 34 year old white housewife She is presented with lesions on the arms and legs of a year's duration, first noticed as painful lumps on both knees Shortly afterward the patient underwent a cesarean section During her hospitalization many new lesions appeared on the outer aspects of the arms Since that time others have developed with less frequency on both the arms and the thighs They are painful for the first few days, but the discomfort gradually disappears and the size of the lesion decreases A small tumor remains palpable under the skin to mark the site of each for varying periods of time

The medial aspect of the right arm discloses two small subcutaneous tumors of about 1 cm in diameter The skin overlying these nodes is dull red A similar lesion is present on the lateral surface of the right thigh Several smaller subcutaneous masses without overlying redness are palpable on both thighs

The Hinton reaction of the blood was negative The hemoglobin content of the blood was 13.3 Gm per hundred cubic centimeters, and the white cells numbered 8,500 per cubic millimeter, a differential smear of the blood was normal The blood sedimentation rate was 13.5 mm per hour A biopsy showed "panniculitis" Treatment has consisted of sulfapyridine given by mouth, 0.5 Gm four times daily, for several weeks

DISCUSSION

DR MAURICE J STRAUSS I agree that this patient has panniculitis, the biopsy certainly showed necrosis of subcutaneous fat On the other hand, I cannot agree that it is a case of relapsing febrile nonsuppurative panniculitis or Weber-Christian disease I say that because it leaves no atrophic scars, and does not show any other symptoms of that disease, except simple panniculitis

DR ALFRED HOLLANDER We should investigate what laxatives the patient may have taken It may be a dermatitis due to phenolphthalein

DR S J MESSINA No drug was taken

DR ALFRED HOLLANDER She said she took Senna

DR WALTER F LEVER The early lesion that is present today has a clinical appearance consistent with that of Weber-Christian disease, although all previous lesions have disappeared without resultant atrophy Weber-Christian disease is becoming more widely recognized So far 31 cases have been described, most of them in the last few years Its cause is not known In some cases new

lesions could be produced by the oral administration of iodine, but phenolphthalein has not been described as a causative agent

Dr S J MESSINA The severity of panniculitis determines the amount of atrophy This is the second of 2 cases of Weber-Christian disease recently seen in one week at the skin clinic of the Massachusetts Memorial Hospital

Dr WALTER F LEVER In the second of the 2 cases of Weber-Christian disease that Dr Cummins and I described (*ARCH DERMAT & SYPH*, 38 415, 1938) many of the lesions disappeared without leaving a trace

A Case for Diagnosis (Sarcoidosis? Scleroderma?) Presented by Dr M M TOLMAN, Boston

Poikiloderma Reticulare (Civatte) Presented by Dr WALTER F LEVER, Boston

H M is a 38 year old married white man employed as a clerk He has an eruption on the forehead and the sides of the face and neck of four years' duration The patient had noticed during that time a gradually progressive discoloration of the skin in the aforementioned areas He stated that there had been some degree of discomfort, consisting of a burning sensation Excessive exposure to sunlight was denied For the past three years this man has taken sulfonamide drugs during the winter months

Examination reveals changes on the sides of the neck, the lateral aspects of the face and to a lesser extent on the forehead, consisting of a dusky red to coppery hued discoloration with an admixture of brownish pigmentation This disturbance is reticular in appearance, because the pilosebaceous orifices are spared Numerous telangiectases are present within the areas of discoloration

A biopsy disclosed hyperpigmentation of the basal cell layer and a moderate degree of hyperkeratosis

DISCUSSION

Dr ALFRED HOLLANDER The disease in this case closely resembles that which Civatte described in women It is not Riehl's melanosis I believe that this man acquired his pigmentation from exposure to sunlight, after having applied something to his skin Cosmetic preparations have led to pigmentation in many instances of light sensitivity

Dr BERNARD APPEL The patient was apparently taking sulfonamide drugs as a cold preventive or treatment in the winter, but the eruption appeared in the summer

Dr ALFRED HOLLANDER I believe that it is a matter of light sensitivity

Dr BERNARD APPEL Do you interpret melanosis as vitamin deficiency?

Dr ALFRED HOLLANDER This picture is similar to that in cases of tar melanosis seen at the end of the first world war In Riehl's melanosis one sees histologically a layer free of pigment in the upper part of the cutis, just next to the epidermis I could not observe it in the presented slide

Dr LEON BABALIAN Poikiloderma reticulare of Civatte is not recognized by every author as an entity According to Petges (*Darier, J, and others Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol 6, pp 116, 119, 134 and 135*) it is only a form, localized on the face, of poikiloderma atrophicum vasculare of Petges-Jacobi The latter condition presents variable aspects If, generally speaking, it is erythema with telangiectasia and evolution toward a pigmented network and atrophy, there exist attenuated conditions which can-

not be distinguished from those described by Civatte on the face. Both conditions have in common their endocrine origin and their chronic evolution. Riehl's melanosis differs from them by its chocolate brown pigmentation, its follicular keratosis and its causative factors (wartime conditions and handling of impure oils).

DR. WALTER F. LEVER. Poikiloderma atrophicans vasculare of Pctges and Jacobi is an entirely different disease from poikiloderma reticulare of Civatte. Poikiloderma atrophicans vasculare appears to represent a secondary atrophy of the skin occurring most frequently in dermatomyositis and scleroderma, but occasionally also in mycosis fungoides. Civatte described his poikiloderma reticulare in 1923 (*Ann de dermat et syph* 4 605, 1923), but, in 1935, in a letter to Kinnear (Kinnear, J. A Case of Riehl's Melanosis. With notes on the Classification of the Poikilodermas. *Brit J Dermat* 47 191, 1935), he stated that he regarded his poikiloderma reticulare as identical with Riehl's melanosis. Nevertheless, several authors still regard the two diseases as different and, I believe, with justification. The differences, as pointed out by Pierini and Bosq (*Ann de dermat et syph* 9 381, 1938), are: first, a reticular pattern is present in Civatte's poikiloderma which is absent in Riehl's melanosis; second, there are telangiectases found in Civatte's poikiloderma, but not in Riehl's melanosis. In this connection I might mention a paper that has just been published in Switzerland (Storck, H. Ueber Riehl's Melanose, *Dermatologica* 92 246, 1946). In this paper the statement is made that the number of cases of Riehl's melanosis had increased during World War II, but, in contrast to World War I, the majority of cases was reported from France rather than from Germany and Austria, possibly because of the nutritional situation which existed in France.

Bernard Appel, M.D., President

G. Marshall Crawford, M.D., Secretary

Dec 4, 1946

Generalized, Progressive Scleroderma Presented by DR. JOHN G. DOWNING, Boston

J. C., a 33 year old white woman of Polish birth, occupied as a drill punch operator, has a dermatosis of two years' duration affecting the face, neck, back and extremities. This is composed of irregular, nonelevated, red patches of assorted sizes and shapes. The color is due to pronounced telangiectasia, which fades completely under pressure. In some areas, particularly the elbows and hands, the skin is thickened, taut and fixed to underlying structures. The skin of the fingers is smooth, shiny and boardlike, resulting in flexion contracture of the digits.

Examination of the blood revealed 3,570,000 erythrocytes per cubic millimeter and a hemoglobin content of 11 Gm., the leukocyte count and differential smear were normal. The calcium content of the blood serum was 9.86 mg. and the phosphorus was 3.4 mg. per hundred cubic centimeters. The Hinton reaction of the blood was negative. The urine was normal. There had been no treatment.

Generalized, Progressive Scleroderma Presented by DR. BERNARD APPEL, Lynn, Mass.

L. W., a 31 year old white American-born fur salesman of Latvian-Russian parentage, has an eruption of eight years' duration, affecting the face, chest

and extremities. The first symptom noticed by the patient was stiffness of his fingers. The first discernible lesion appeared on the back of the right hand eight years ago. This consisted of a small, hard, white spot which spread slowly but steadily. A similar area soon appeared on the other hand, more followed on all of the fingers and later on the feet and legs. Within the past two years the face and chest have become affected. There has been some difficulty in swallowing in the last twelve months.

There is a moderate degree of thickening of the skin of the face. Irregular atrophic areas are noted on the chest and legs, surrounded by a dusky purplish fringe. The skin of the hands, the feet and the ankles is thin, hard and firmly bound to the underlying tissues. There is loss of hair and diminution of sweating in these areas. The fingers are boardlike in hardness and semiflexed in a fixed position. Telangiectasia are seen to some extent on all of the aforementioned areas.

Dihydrotachysterol was administered (1 cc daily) for five months, but was not taken with regularity. The reaction to the Sulkowitch test for calcium in the urine was usually positive (1 plus) during treatment. The patient thinks that swallowing is somewhat easier and that the skin of his fingers is not as tight. The calcium content of the blood serum was normal before therapy with dihydrotachysterol and after five months of this medication, the serum phosphorus decreased from 3.5 mg to 2 mg per hundred cubic centimeters (normal 3.0 to 4.5 mg).

Generalized, Progressive Scleroderma Presented by DR GEORGE E. MORRIS, Boston

A 42 year old white French-Canadian housewife, G. L., has generalized cutaneous changes of eighteen months' duration. The first manifestation was painless ulcers on her finger tips and heels, which required several months to heal. During the past year there has been mild generalized itching accompanied with darkening of the skin and progressively increasing stiffness of the hands and feet. It has been difficult for the patient to open her mouth for the past six months. Shallow ulcers have continued to appear on the finger tips, knuckles, toes and ankles, as these heal, the surrounding skin becomes thick and hard.

The Hinton reaction of the blood was negative. The white cells of the blood numbered 10,600 per cubic millimeter, the differential smear was normal. The urine was normal. The reaction to the Sulkowitch test was positive (1 plus). The chloride content of the blood serum was 74 milliequivalents per liter (normal 100 to 106), the sodium was 133 milliequivalents per liter (normal 136 to 145), and the calcium was 10.8 mg per hundred cubic centimeters. The basal metabolic rate was -33 per cent. Roentgen examination of the bones revealed nothing abnormal except mild decalcification of the small bones of the wrists. Therapy consisted of administration of dihydrotachysterol, 5 drops twice a day for two weeks prior to presentation, the reaction to the Sulkowitch test was then 2 plus.

Generalized, Progressive Scleroderma Presented by DR S. J. MESSINA, Boston

J. W., a 50 year old white American woman, a housekeeper, has a cutaneous disturbance involving the shoulders, chest and extremities of six months' duration. These changes began on the upper part of the chest and extended to the shoulders, when first noted, the skin appeared somewhat darkened and thicker than normal. Shortly afterward the arms, thighs and legs became affected. There has been slow progression in all areas, with some lightening in color.

Examination reveals irregular involvement of the upper part of the chest, shoulders, lateral region of the arms, anterior area of the thighs and legs. The

lesions vary from the size of a palm to double that of a hand and are all sharply defined. The skin within these areas is nonelevated, smooth, ivory colored and thickened, with a purplish border.

A biopsy specimen revealed histologic changes characteristic of scleroderma. The Hinton reaction of the blood was negative. The urine was normal. The reaction to the Sulkowitch test was positive. A roentgenogram of the chest was normal. The basal metabolic rate was +10 per cent. The hemoglobin content of the blood was 12.6 Gm per hundred cubic centimeters, and the leukocytes numbered 7,900 per cubic millimeter. The calcium content of the blood serum was 11.61 mg per hundred cubic centimeters when first examined. The patient then received 1 cc of dihydrotachysterol daily for a period of six weeks and thereafter a dose of 2 cc daily for another six weeks. The calcium content of the blood serum was determined at two week intervals and was not notably affected, after two months of therapy it was found to be 11.76 mg per hundred cubic centimeters. Slight but detectable improvement has occurred.

Localized Scleroderma (Morphea). Presented by DR JOHN G DOWNING, Boston

A 17 year old white American girl student, B F L., has a dermatosis of three years' duration, affecting the neck and arms. The first changes appeared on the right side of the neck, and at a later date the arms became involved. There has been little or no extension of the process since it first appeared, and the lesions have been essentially asymptomatic. The patient associates the onset of her disease with diphtheria immunization which took place three years ago.

There are three areas of involvement: one on the right side of the neck and one on the lateral aspect of each arm. In the right supraclavicular region is a palm-sized, sharply defined, white, atrophic lesion with an ivory-colored, finger-like band extending to the front of the neck. The lateral aspect of each arm presents a linear lesion about 1 by 5 inches (2.5 by 13 cm) in size. The skin in these areas is somewhat thickened and hyperpigmented.

The Hinton reaction of the blood was negative. The urine was normal. The reaction to the Sulkowitch test was positive (2 plus). The calcium content of the blood serum was 8.95 mg per hundred cubic centimeters. Treatment has consisted of administration of 0.5 cc of dihydrotachysterol daily for ten days and thereafter 2.5 cc daily for a period of five weeks. After the first ten days the serum calcium had risen to 9.94 mg and after one month to 9.96 mg per hundred cubic centimeters. There has been some softening of the lesions.

DISCUSSION

DR JOHN G DOWNING. In these 5 cases there is probably a complete picture of scleroderma, with examples of the localized, linear, acrosclerotic and diffuse types. An unusual feature in the first case is the erythematous macules on the face and arms. Looking at it superficially, one might think of lupus erythematosus, but more careful examination reveals dilated capillaries. It is a question whether this indicates that the disease will rapidly become generalized. I believe that this vascular dilatation warns of accelerated progress. The patient also has signs of Raynaud's disease. For three years before the onset she was a punch press operator, and one encounters considerable vibration in this occupation. During the war there developed numerous cases of "dead fingers" among persons working with various vibrating tools. Two of today's patients improved slightly while taking dihydrotachysterol ("A T-10"). When first examined, the 50 year old woman (J W) showed many lesions of morphea type, surrounded by a wide

violaceous band of edema Shortly after she took the dihydrotachysterol this edema disappeared and the violaceous color was replaced by pigmentation The 17 year old girl (B F L) with morphea has improved This could be spontaneous involution, but it seemed to follow too soon after the treatment to be a coincidence I have used thyroid extract in a few cases of localized scleroderma with good results One girl with linear involvement of one arm was treated with neostigmine with apparent cure One cannot say that dihydrotachysterol ("A T -10") therapy is the only treatment, because success has also followed other therapy

DR E F FINNERTY (by invitation) My co-workers and I have been studying the action of dihydrotachysterol and the occasional association of scleroderma with hyperparathyroidism In the latter there is probably an increase in the viscosity of the blood causing some anoxia of the tissues In hypoparathyroidism there may be vasospasm resulting in the same tissue anoxia This decreased tissue oxygenation seems to be the important change, whether due to an increase in blood viscosity or to vasospasm We have also studied a third group of patients with a tendency to hypoparathyroidism who are on a low vitamin D and low calcium diet and may eventually be the same as hypoparathyroid patients, with vasospasm and anoxia Every patient with scleroderma should be studied to determine whether they are hyperparathyroid or hypoparathyroid, if parathyroid function seems normal the patients might fit into this third class Blood viscosity determinations alone are of little value because of the wide range of normal readings, but information as to the amount of ionic calcium is helpful This is found by the serum calcium and total protein of the same blood specimen plotted on McLean's normogram (McLean, F C, and Hastings, A B *Am J M Sc* 189 601, 1935)

DR WALTER F LEVER The action of dihydrotachysterol is similar to that of large doses of vitamin D In both instances there is an increased absorption of calcium into the blood either from the intestine, if sufficient calcium is provided in the diet, or from bones and tissue, if calcium intake is low This increased absorption into the blood causes hypercalcemia and leads to an increased elimination of calcium through the kidneys If the intake of calcium in the diet is low, both dihydrotachysterol and large doses of vitamin D will produce a negative calcium balance Cornbleet (*ARCH DERMAT & SYPH* 35 188, 1937) treated a group of patients with scleroderma with high doses of vitamin D I think that it is the same as treatment with dihydrotachysterol Cornbleet stated that he found in scleroderma a positive calcium balance, which he explained as due to the retention of calcium in the tissues affected with scleroderma By giving large doses of vitamin D he converted the positive calcium balance into a negative calcium balance He postulated that this calcium, instead of being retained in the affected areas, was eliminated through the kidneys That would provide an explanation of the benefit one may obtain with either vitamin D or dihydrotachysterol therapy in scleroderma I did not understand whether you treated patients with hyperparathyroidism as well as those with hypoparathyroidism Did you give both groups dihydrotachysterol, or only the hypoparathyroid patients?

DR E F FINNERTY (by invitation) Hyperparathyroidism should be remedied surgically Some of these patients have been treated for five months, and our study has been carried on only during the past month, so that we have too little data to speak more fully

DR JOHN G DOWNING I think that this work will be worth while An excellent symposium on scleroderma by Burch (*New Orleans M & Surg J* 92 6, 1939) reviewed all of the theories concerning this disease The first patient in today's group was seen by the surgical service, and a sympathectomy was advised Two of my patients have had sympathectomies, neither was improved by this

procedure The tissue anoxia studies may help to determine whether these patients will need parathyroidectomy or sympathectomy, or perhaps neither I believe that in my patients who underwent sympathectomy and did not respond to treatment the disease had gone beyond the functional stage It had become an organic disease of the vessels and tissues, and by the time sympathectomy was done it was too late An early approach might be beneficial

DR M C HANSON (by invitation) It should be pointed out that the action of dihydrotachysterol (vitamin D₂) is more similar to that of parathyroid hormone than vitamin D₃, except when the latter is given in toxic doses The serum calcium level apparently does not play too great a part, for it is usually normal as in the cases presented There must be some disturbance in the tissues themselves that determines the unusual deposition of calcium

DR FRANCIS M THURMON S J Thannhauser stated the belief that scleroderma is primarily a vascular disease (personal communication)

DR ADRIAN H SCOLTEN I would like to know what danger there is in one's giving dihydrotachysterol I understand that in the treatment of pemphigus it has caused some deaths

DR E F FINNERTY (by invitation) Dihydrotachysterol is supposed to act in a manner similar to parathyroid substance It supposedly first increases the excretion of phosphorus in the urine, according to the Albright theories (Goodman L, and Gilman, A The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1940, p 1287), which will diminish serum phosphorus and will raise the serum calcium and so increase the calcium output in the urine Also, presumably it acts directly on the bone by removing calcium as parathyroid hormone does, and the toxic effects would be similar to hyperparathyroidism

DR WALTER F LEVER Several years ago I treated patients with pemphigus by large doses of dihydrotachysterol (ARCH DERMAT & SYPH 43 341, 1941), but in recent years have used large doses of vitamin D instead (New England J Med 231-44, 1944) Both drugs, if given in excess, cause the same toxic manifestations excessive hypercalcemia and renal insufficiency Excessive hypercalcemia may progress to coma and death The renal tubules may be blocked by calcium deposits, resulting in an elevation of the nonprotein nitrogen of the blood serum An elevation of the nonprotein nitrogen to 40 or 50 mg per hundred cubic centimeters is reversible If large doses are continued, the blocking of the tubules may lead to uremia and death The safest way to prevent damage from dihydrotachysterol or vitamin D is to check the serum calcium and nonprotein nitrogen every five days A dose of 1 to 25 cc. of 0.5 per cent dihydrotachysterol daily would not cause harm in young patients, but, in old persons, in whom the capacity of the kidneys is less, or in patients whose renal function is already impaired, this amount might be dangerous if given for a long period of time

DR M C HANSON Would you consider a sudden rise in the calcium a danger sign? Is it constant?

DR WALTER F LEVER The rise of the serum calcium and nonprotein nitrogen is gradual, not sudden If the serum calcium rises to 13 mg per hundred cubic centimeters, or the nonprotein nitrogen rises to 45 mg per hundred cubic centimeters, the dihydrotachysterol should be temporarily discontinued For several days after the omission of dihydrotachysterol the serum calcium and nonprotein nitrogen may continue, then they will gradually return to normal, usually within two weeks

DR ALFRED HOLLANDER, Springfield, Mass In regard to the toxicity of dihydrotachysterol it will be worth while to read the papers of F Holtz of

Germany, who has done more work with it than anyone in this country (*Arch f exper Path u Pharmacol* **174** 51, 1933, *Arch klin Chir* **177** 32, 1933, *Deutsche Ztschr f Chir* **242** 521, 1934, *Klin Wchschr* **13** 104, 1934, and *Deutsche med W chnschr* **15** 560, 1934)

A Case for Diagnosis (Pemphigus Vegetans? Dermatitis Herpetiformis? Pityriasis Lichenoides et Varioliformis Acuta?) Presented by DR C GUY LANE, Boston

A Case for Diagnosis (Eosinophilic Granuloma of the Skin? Drug Eruption? Lupus Erythematosus?) Presented by DR JOHN G DOWNING, Boston

Gangrene of Toes, Due to Raynaud's Disease Presented by DR H BERTRAM ULLIAN, Everett, Mass

Mycosis Fungoides Presented by DR JOHN G DOWNING, Boston

DISCUSSION

DR JOHN G DOWNING I recently presented a case of lymphoblastoma treated with radioactive phosphorus (*ARCH DERMAT & SYPH* **57** 601 [March] 1948) The woman was suffering with itching, burning and loss of sleep After she was given radioactive phosphorus, there was a remarkable response of the skin and she was very comfortable, but aplastic anemia developed and the patient died two months ago Since then my co-workers and I have treated 2 more patients with mycosis fungoides with the same agent It is our opinion that radioactive phosphorus should be used only when the disease is in the advanced stages and everything else has been tried Any means of therapy, such as radioactive phosphorus, that will lengthen life by two or three years with more comfort is justifiable In a case like this, when the skin is apparently in fairly good condition, it is better not to use radioactive phosphorus but to use therapy that we have used for years, with which patients have obtained a certain amount of relief, such as roentgen radiation When there is no further response to roentgen therapy, it would be justifiable to use radioactive phosphorus In time, we will know more about the use of this medication and may achieve better results

DR FRANCIS M THURMON The same situation exists with respect to nitrogen mustard, which is now being used for blood dyscrasias I have seen it employed in 2 cases of mycosis fungoides without benefit

A Case for Diagnosis (Syphilis of Skin, Tertiary?) Presented by DR F M THURMON, Boston

Erythroderma Ichthyosiforme Congenitum in a 17 Year Old Boy Presented by DR JOHN G DOWNING, Boston

A Case for Diagnosis (Urticaria Pigmentosa?) Presented by DR ROBERT H GOLDFARB, Boston

URTICARIAL REACTION INDUCED IN THE DOG BY INTRAVENOUS INJECTION OF SORBITOL MONOLAURATE

A C IVY, M D, Ph D
CARLOS A TANTURI, M D*
R HERNANDEZ, M D
AND
E BAROSO, M D
CHICAGO

DURING the course of experiments on parenteral nutrition in the dog, H C Meng and Smith Freeman¹ observed that the slow intravenous injection of a fat emulsion, stabilized with sorbitol monolaurate (tween 20²), was associated with the development of urticaria. This observation prompted us to undertake a study of the changes which might be related to the development of urticaria, since no other pure substance is known to us which on intravenous injection will consistently cause urticaria. The chemical does not cause urticaria when given orally but does so when introduced intradermally, without previous sensitization of the animal.

In order for one to determine the relation of this experimental urticaria in the dog to that which is produced in man, it will be necessary to review briefly what is known regarding the nature of urticaria in man.

SUMMARY OF KNOWLEDGE OF THE URTICARIAL REACTION

The urticarial reaction consists essentially of three local changes in the skin, which Lewis^{1a} has referred to as "the triple response." The triple response consists (1) of a red area, which within a few seconds becomes surrounded (2) by a flare or flush, after which (3) a wheal begins to appear. The wheal soon becomes pale and usually disappears within an hour.

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From the Department of Physiology, Northwestern University and the Department of Clinical Science, University of Illinois

¹ Meng, H C, and Freeman, S. Experimental Studies on the Intravenous Injection of Fat Emulsion into Dogs, *J Lab & Clin Med* **33**:689-707, 1948

^{1a} Lewis, T. *The Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, 1926

This triple response may be produced experimentally in human skin, and in the skin of some animals, in response to mechanical injury, heat and cold and the intracutaneous introduction of many substances, such as histamine, allergens, morphine, codeine, physostigmine, pilocarpine and atropine. It is generally agreed, however, that whealing is a specific response to certain substances, because all substances do not give the response.

Histologic Characteristics—Histopathologically, the urticarial reaction is a mild inflammation² which is remarkably reversible, since the production of a morphine wheal thirty-five times at the same site over the period of several days did not produce any evidence of chronic histologic change.^{2d} When the reaction is produced by the intradermal introduction of ragweed pollen into a person sensitive to this pollen, the changes which occur are as follows. After five minutes the blood vessels are engorged, slight edema is evident, and a few leukocytes have collected in the engorged minute vessels. After ten minutes the edema has increased to a maximum and there is pronounced intravascular collection of polymorphonuclear leukocytes. After fifteen minutes there is moderate engorgement except in pale areas, edema is appreciable, and wandering cells and leukocytes are in the surrounding tissues, 25 per cent of the leukocytes are eosinophils. After twenty minutes the principal addition to the prior changes is an increase in eosinophils to 50 per cent. At a variable time after four hours according to Kline and associates^{2b} and after twenty-four to forty-eight hours according to Berger and Lang,^{2c} the eosinophils have appreciably decreased in number.

Histamine introduced intradermally into allergic persons tends to produce histopathologic changes like a specific allergen,^{2b} whereas in the nonallergic person it causes vascular changes and edema and very little leukocytosis.

The intravascular behavior of leukocytes in an antigen-antibody reaction in the rabbit, as demonstrated by Abell and Schenck,^{1e} is of much interest. When horse serum is applied to the minute vessels of the ear of a sensitized rabbit, the vessels being visualized by a special technic, the vascular endothelium develops stickiness for leukocytes, which collect in clumps and pass through the wall of the vessel. This behavior is significant because leukocytes contain histamine and thromboplastin.

2 (a) Numa, P. G. *The Histopathology of Diseases of the Skin*, New York, Macmillan and Company, 1896. (b) Kline, B. S., Cohen, M. B., and Rudolph, J. A. *J. Allergy* **3** 531, 1932. (c) Berger, W., and Lang, T. J. *Ztschr. f. Hyg. u. Infektionskr.* **113** 206, 1936. (d) Torok, L., and Hare, P. *Arch. f. Dermat. u. Syph.* **65** 2, 1903. (e) Abell, P. G., and Schenck, H. P. *J. Immunol.* **34** 195, 1938.

Physiologic Aspects Physiologically, the mechanism of the formation of the red spot, the surrounding flare and the wheal has been studied extensively, particularly by Lewis and his colleagues¹

The red spot surrounding the site of introduction of the urticarigenic agent is due to the direct dilating action of the agent, or something produced by the agent, on the blood vessels. It occurs in the denervated skin after time has elapsed to permit degeneration of nerve fibers¹

The diffuse flare surrounding the red spot and, later, the wheal, is due predominantly³ to an axon reflex, since it occurs in an area of skin during the first five or six days after section of its nerve supply, but not afterward, the wheal but not the flare occurring then¹

The wheal, which begins soon after the appearance of the flare, is usually confined to the area of the red spot or to those vessels most directly influenced by the injected agent or something produced by it. The wheal is due to an increase in capillary permeability. This fact is shown by the coloring of the wheal after the intravenous injection of dyes (trypan blue or trypan red, congo red, Evans blue and rose bengal), which ordinarily do not stain the skin⁴. This coloring occurs only if the dyes are injected intravenously soon before or at the time the wheal forms. It fails to occur if the dye is injected after the wheal has turned pale because of vascular occlusion secondary to the presence of the edema. The increased permeability is also demonstrated by the presence of protein in the wheal fluid in a concentration which approximates that of plasma⁵. Formation of a wheal is not due to local vasodilatation, per se, because intense local dilatation may be caused by the introduction of methacholine chloride (mecholyl chloride®) or acetylcholine by needle or electrophoresis without the formation of a wheal or a change in permeability⁶. The formation of the wheal is not due to increased pressure in or distension of the capillaries. One can demonstrate the validity of this statement easily by placing a sphygmomanometer cuff on the arm, raising the pressure in the cuff up to 30 or 50 mm of mercury and then introducing histamine into the skin¹. This procedure, of course, increases the venous and capillary pressure, yet

3 Goldschmidt, S, and M'Glone, B. Proc Soc Exper Biol & Med **29** 827, 1932

4 Ebbecke, U. Klin Wchnschr **2**:1725, 1923. Hoff, F. Ztschr f d ges exper Med **57** 253, 1927. Ferreebe, J. W., and Berliner, P. W. Proc Soc Exper Biol & Med **46** 549, 1941.

5 Lewis¹ Torok, L. Arch f Dermat u Syph **53** 243, 1900. Stead, E. A., and Warren, J. W. J Clin Investigation **23** 279, 1944.

6 (a) Rocha E. Silva, M., and Dragstedt, C. A. J Pharmacol & Exper Therap **73** 405, 1941. (b) Last, M. R., and Loew, E. R. ibid **89** 81, 1947. (c) Alexander, H. L., Elliott, R., and Kirchner, E. J Invest Dermat **3** 207, 1940.

the wheal is the same or smaller in size than usual, and it becomes progressively smaller until the systolic pressure is reached. On complete occlusion of the blood supply the wheal does not occur, but if the occlusion is released within five minutes after the introduction of histamine the wheal occurs. The results of such experiments as those just described unequivocally prove (a) that the wheal is associated with the local increase in permeability of the capillaries, (b) that its formation is dependent on an adequate flow of blood and (c) that its formation is not dependent solely on a high venous pressure.

In whealing, the lymphatics also become more permeable, and their efficiency of drainage is decreased by the pressure block caused by the edema fluid.⁷

Some animals do not manifest whealing. Wheals do not develop in rabbits, cats and guinea pigs when histamine or other wheal-producing substances are introduced intradermally.⁸ In the dog, goat, horse and man, they do. However, histamine increases the permeability to dyes of the capillaries in rabbits, cats and guinea pigs. Whether this failure of certain animals to manifest whealing is due to structural or to physiologic differences in the skin is uncertain.

Some substances cause local vasodilatation without flare and whealing, regardless of concentration. Other substances and procedures cause vasodilatation without whealing when the concentration or intensity is relatively high. This difference could be explained as due to the possibility that some substances or procedures are more injurious to the capillary wall than are others.

The concept that the wheal and flare are due to the release of a substance by the cells of the skin when they are injured was derived from many experiments performed by Lewis.¹¹ We shall cite a few of his experiments. The circulation to the arm is impaired first with a pressure of 30 mm of mercury to cause congestion and then to 200 mm mercury for occlusion, histamine is introduced intradermally, the skin is covered with petrolatum U S P and warmed to 20 C with water and the histamine theoretically is permitted to diffuse for five minutes. During the occlusion a small area of local vasodilatation occurs at about the point of injection, and on release of the occlusion the area doubles in size, this development obviously indicating that diffusion has occurred. Now, if the experiment is repeated, the skin of an urticarial subject having dermatographism being stroked, the purple line formed by the stroke, as well as the wheal which occurs after release of the occlusion, can be seen to spread. Also, if two wheals and

7 (a) Hudack, S, and McMaster, P D. *J Exper Med* **56** 223, 1932, **57** 751, 1933. (b) Abramson, H A, and Engle, M. *J Invest Dermat* **1** 65, 1938.

8 Darsie, M L, Perry, S M, Rosenfeld, D, and Zaro, J D. *Proc Soc Exper Biol & Med* **59** 278, 1945.

flares are produced on an arm, one above the other, and the circulation to the lower one is occluded, the flare of the one without occlusion will fade, while the other flare will persist until the occlusion is released. This experiment shows that the cause of the flare is either washed away or destroyed by the blood. To show that a vasodilator substance may enter the blood in urticaria, in a patient with urticaria factitia the smallest dose of histamine given subcutaneously which would cause flushing of the skin was determined. The skin of the patient was then stroked to produce whealing in several areas, and flushing occurred. There are also a number of articles in the literature which show that whealing of the skin produced by various means, mechanical and caloric,⁹ stimulates gastric secretion. The foregoing experiments indicate the formation of a substance that diffuses rather rapidly. Lewis and his colleagues performed another experiment in which it was found that a more slowly diffusing substance was produced. When a restricted area of the skin is exposed to an erythema dose of ultraviolet light, the red area is much larger at twenty-four than at six hours.

Thus there is evidence which indicates that on injury of the cells of the skin (*a*) a rapidly diffusing substance analogous to histamine, which dilates and increases the permeability of minute blood vessels, is formed, and (*b*) a slowly diffusing substance (H colloid) may be formed. It need not be assumed on the basis of the evidence that only histamine or only one H substance is produced.¹⁰ The nature of the vasodilator may vary with the agent involved in its production. That this statement is true is indicated by the results of experiments performed on refractoriness and antihistaminic drugs, to be mentioned later.

Is histamine directly involved in causing the flare and wheal? Histamine is present in the skin.¹¹ Lewis and his colleague^{1a} were able to obtain enough wheal fluid to demonstrate on its injection into the skin the occurrence of a flare and wheal like those caused by histamine. But Abramson and Engle^{7b} were unable to isolate histamine from

9 Baker, T. W. Histaminase in Treatment of Cold Allergy, *J. A. M. A.* **114** 1059 (March 23) 1940. Horton, B. T., Brown, G. E., and Roth, G. M. Hypersensitiveness to Cold, with Local and Systemic Manifestations of Histamine-Like Character. Its Amenability to Treatment, *ibid.* **107** 1263 (Oct. 17) 1936.

10 Krogh, A. The Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1929. Rous, P., and Gilding, B. M. *J. Exper. Med.* **51** 27, 1930.

11 Best, C. H., and McHenry, E. W. *Physiol. Rev.* **11** 379, 1931. Rose, B., and Brown, J. S. L. *Am. J. Physiol.* **124** 412, 1938. Rosenthal, S. P., and Minard, D. *J. Exper. Med.* **70** 415, 1939. Marshall, P. B. *J. Physiol.* **102** 180, 1943. Alexander, F. *Quart. J. Exper. Physiol.* **33** 71, 1944.

wheals caused by ragweed pollen. They do not interpret this finding as proving that histamine is absent from the fluid or the process which caused the whealing. Nevertheless, there is no direct evidence that histamine is released in the urticarial reaction.

Is acetylcholine directly involved in causing the flare and wheal? Grant, Pearson and Comeau¹² suggested that cholinergic nerves were involved in the urticaria which occurs in association with emotion, exercise and warmth. They made this suggestion because in such conditions urticaria could be induced by pilocarpine and choline derivatives and improved by atropine. However, considerable evidence has been presented against the view that acetylcholine is concerned in the mechanism of the production of urticaria. Acetylcholine introduced into the skin by electrophoresis causes only local vasodilatation.¹³ It has not been demonstrated that acetylcholine is produced by antidromic (posterior root nerves) or axon reflex impulses.¹³ Atropine has no effect on the wheal and flare induced in man by allergens.¹⁴ On the contrary, Lewis¹⁵ more recently reported that wheals develop in many women on the electrophoretic introduction of acetylcholine. It is possible that in a susceptible person the vasodilatation induced locally by acetylcholine predisposes to the development of a wheal in the same way that vasoconstriction tends to reduce whealing.¹⁶ On the basis of the evidence, it is a likely hypothesis that the release of acetylcholine is a part of the causative mechanism of urticaria associated with exposure to emotion, exercise and warmth.

Refractoriness to Triple Response—Due to Histamine. Lewis¹² showed quite clearly that for a period from fifteen up to thirty or sixty minutes after blood vessels have been exposed locally to the action of histamine the vessels are refractory to a second exposure to histamine as regards formation of the wheal but not of the flare. For example, if the blood supply of an arm is occluded, and histamine is introduced intradermally at site A and site B, and the arm kept warm at 33 C for fifteen or twenty minutes, and then, before the occlusion is released, histamine is introduced again into site B but not into site A on release of the occlusion, a wheal does not occur at site A, and no wheal, or only a slight one, occurs at site B, though a flare occurs. This experiment shows that the vessels at site B have become refractory to whealing but not to flare.

12 Grant, R. T., Pearson, R. S. B., and Comeau, W. J. *Clin. Sc.* **2**: 253, 1936.

13 Doupe, J., Cullen, C. H., Macaulay, L. J., Sharp, M. E., Barnes, R., and Kerr, A. S. *J. Neurol. & Psychiat.* **6**: 94, 1943.

14 Tuft, L., and Brodsky, M. L. *J. Allergy* **7**: 238, 1936.

15 Lewis, T. *Clin. Sc.* **5**: 5, 1944.

16 Loew, C. R. *Physiol. Rev.* **27**: 542, 1947.

If a histamine wheal and flare are induced in the same site every thirty minutes, the site becomes refractory to whealing¹⁷ If an hour elapses between the induction of the wheal and that of the flare, the site does not become refractory to whealing after 10 or 12 trials, whether the histamine is introduced by needle or by electrophoresis¹⁷

Thus, refractoriness to the effect of histamine in increasing the permeability of capillaries lasts only ten to thirty minutes

Due to a Mechanical Stimulus If a stroke stimulus is applied to the skin of a patient with urticaria factitia and then, fifteen or thirty minutes later, when the wheal has started to subside, a second stroke is applied so as to intersect the wheal of the first, a wheal does not develop at the intersection The time element in this experiment is analogous to the refractory period of whealing induced by histamine

Due to Physical Agents When the skin is injured by heat, freezing, ultraviolet light or roentgen rays to the point that some erythema and edema result, flare, but not whealing, occurs in response to histamine¹⁸ Shaffer¹⁹ has found that doses of roentgen radiation (125 r) which do not cause visible injury induce a refractoriness to histamine whealing forty-eight hours after exposure and continues for four days

Due to Allergens In patients with chronic urticaria wheals do not ordinarily occur in the same site until thirty hours or more have elapsed Nevertheless, the introduction of histamine into such a refractory site produces a wheal This reaction shows that in this case the blood vessels are not refractory to whealing

However, during the subsidence of a wheal caused by an allergen (fish), the site is refractory to histamine for ten or twenty minutes Similarly, during the subsidence of a wheal caused by intradermally administered histamine, the site is refractory to an allergen²⁰

This evidence shows that there is one stage of refractoriness to an allergen which is not due to the inability of the capillary to react to histamine by wheal formation but is probably due to the failure of the allergen to react with the cells to produce an H substance

Due to Urticariogenic Drugs Other Than Histamine Alexander, Elliott and Kirchner^{6c} reported some very interesting observations on refractoriness, which are basic First, they find that refractoriness is a quantitative reaction, i e, whealing may not occur at one period of recovery from whealing when the previous concentration of drug is used, but may occur in response to a stronger concentration Second, they find that urticariogenic drugs may be grouped as regards the

17 Alexander, Elliott and Kirchner^{6c} Cooke, R A J Immunol 7 219, 1922

18 Lewis^{1a} Zurhelle, E Dermat Ztschr 72 129, 1935

19 Shaffer, B J Invest Dermat 3 159, 1940

20 Hare, R Heart 13 227, 1926

length of their refractory period. For example, drugs in group A, such as pilocarpine and physostigmine, render the skin unresponsive to a second application of the drug for a longer period (forty-eight hours) than do drugs in group B, such as codeine, morphine and atropine (twelve to twenty-four hours), and drugs in group C, such as histamine (one hour), render the skin unresponsive for a relatively short period. Refractoriness developed in response to pilocarpine and physostigmine is analogous to that developed to an allergen, which fact suggests that these drugs produce H substance only. Codeine, morphine and atropine may produce some H substance and also may act directly on the blood vessels as does histamine, whereas histamine does not release any H substance but acts solely on the blood vessels.

The evidence available on the mechanism of refractoriness to urticariogenic agents shows quite clearly that something other than the production of histamine is involved in most urticarial reactions. Early in the course of recovery from an urticarial reaction the blood vessels are not responsive to histamine, later they are responsive to histamine but not to certain urticariogenic allergens and drugs, and the reason that whealing does not occur apparently is that there is exhaustion of the production of H substance by the cells which react with the allergen.

Action of Antihistaminic Drugs. Antergan® (N,N-dimethyl-N'-phenyl-N'-benzyl-ethylenediamine), neoantergan® (N,N-dimethyl-N'-[p-methoxy-benzyl]-N'-[α-pyridyl]ethylenediamine), diphenhydramine hydrochloride (benadryl hydrochloride®), and tripeleminamine hydrochloride (pyribenzamine hydrochloride®) decrease the experimentally induced histamine flare and wheal when the dose of histamine is minimal and the dose of antihistamine drug is maximal.¹⁶ The antihistamine drugs diminish dermographic responses and responses to intradermally administered antigens and benefit a large percentage of patients with acute and chronic urticaria.¹⁶

Last and Loew^{6b} studied the effect of various urticariogenic agents on the permeability to trypan blue of the blood vessels of the skin of the rabbit. They found that diphenhydramine hydrochloride and neoantergan® prevented or diminished the increased permeability of the dye due to a local injection of histamine. Favorable results were not obtained when trypsin, snake venom, staphylococcus toxin, tetracaine, codeine or horse serum in a sensitized rabbit was used. These negative results may have been due to several causes. First, the dose of the toxic substance may have been too large in relation to the potency of the antihistaminic drug. Second, the increased permeability may have been due to the direct action of the toxic agent on the capillary. Third, an H substance other than histamine may have been produced by the cells. If the first condition exists, a more potent antihistaminic drug is required. If the second does, an agent which will "toughen" or support the capillary

itself is needed. If the third is the case, then anti-H-substances other than antihistaminic compounds will have to be sought.

Antihistaminic drugs may act to decrease the vascular effects of histamine in several ways: (1) by direct action on the vascular endothelium to decrease permeability, (2) by speeding the destruction of histamine or (3) by competing for the cell receptors of histamine. There is no evidence supporting the first two hypotheses. It appears from the evidence that diphenhydramine hydrochloride decreases the action of histamine on blood pressure and intestinal strips by competing for or blocking cell receptors for histamine.²¹ This would imply that diphenhydramine hydrochloride decreases the whealing response to histamine by competing for or covering up receptors concerned in rendering the capillaries more permeable. This action would concern the endothelial cells more than the muscle cells of the peripheral blood vessels, a hypothesis indicating that the reason that recovery of the flare in response to histamine occurs before that of whealing is that the endothelial cells of the capillaries are inactivated for a longer time than are the muscle cells and Rouget cells.

OBSERVATIONS ON SORBITOL MONOLAURATE IN THE DOG

The changes induced by sorbitol monolaurate in the body of the dog resemble those which are associated with peptone and anaphylactic shock, with two definite exceptions. One exception is that when the chemical is injected intravenously (20 to 50 mg) the fall in blood pressure is less precipitous and the greatest concentration of the vaso-depressor substance in the blood plasma is found about ten minutes after the injection. The other exception is that hypercoagulability, rather than hypocoagulability, of the blood occurs after the intravenous injection of the chemical. Refractoriness to the blood pressure-reducing effects of the chemical lasts from four to eighteen hours. A crossed refractoriness between the chemical, peptone and anaphylactic shock is demonstrable. The refractoriness, however, is quantitative and not an "all or none" phenomenon. This evidence may be interpreted as showing that the intravenous injection of the chemical causes the release of two substances: (1) histamine or an H substance and (2) a thromboplastic substance. On the contrary, the vasodepressor and the thromboplastic effects may be due to the same substance.

The foregoing summary is based on experiments too extensive to report here, since this study is primarily concerned with the urticarigenic action of the chemical.

²¹ Wells, J. A., Morris, H. C., Bull, H. B., and Dragstedt, C. A. *J. Pharmacol. & Exper. Therap.* **85** 122, 1945. Halperin, B. N., and Mauris, G.: *Compt. rend. Soc. de biol.* **140** 440, 1946.

Urticaria Produced by Sorbitol Monolaurate—Urticaria was produced in the course of our studies in more than 200 anesthetized or unanesthetized dogs. Urticaria is quite consistently produced by a dose of 1 cc of a 1 per cent solution of the chemical given intravenously or by the intradermal injection of 0.01 to 0.04 cc of a 1:1,000 dilution with an isotonic solution of sodium chloride.

Relation of the Appearance of Urticaria to the Fall in Blood Pressure

In anesthetized animals the fall in blood pressure produced by a dose of 1 cc of a 1 per cent solution is, as a rule, slight (10 to 30 mm of mercury), and recovery occurs within thirty minutes. An occasional dog is more sensitive. In both anesthetized and unanesthetized dogs a generalized or patchy flushing of the skin occurs three to five minutes after the intravenous injection of 1 cc of a 1 per cent solution. This flushing appears at the time the blood pressure starts to fall. The flushing is soon followed by the appearance of typical urticarial wheals (central edema and pallor with peripheral flare). Some of the wheals may become confluent ten to twelve minutes after injection. The wheals begin to disappear after fifteen to twenty minutes and are gone usually in thirty minutes, frequently leaving a slightly reddened patch.

There is a striking relation between the appearance of urticaria and the fall of blood pressure. If the blood pressure in response to the injection of the chemical falls below 80 mm mercury, urticaria does not occur. In 1 dog 0.8 cc of a 1 per cent solution of the chemical caused such a pronounced fall in blood pressure that urticaria did not occur. In an occasional dog 1 cc of a 1 per cent solution causes a slight fall in pressure but not urticaria; in such a case a second injection of 1 cc has never failed to cause urticaria.

In some instances thirty to sixty minutes after the urticaria has disappeared with the injection of 0.8 to 1.0 cc of a 1 per cent solution urticaria may be induced again, provided some fall in blood pressure is obtained. This procedure may occasionally be repeated as many as three times in the course of five or six hours. In the latter cases, the wheals occur at a new site.

Refractoriness—If a repeated injection of the chemical does not lower the blood pressure, because of refractoriness, then urticaria is not obtained. This fact was observed in many cases and indicates that some vasodilator mechanism is involved. However, in such cases the reddened patch remaining from a previous wheal may become redder. In other words, the animal may become refractory to the mechanism responsible for edema but not to local or generalized flushing. The refractoriness disappears after twenty-four hours. If refractoriness is obtained to a dose of 1 cc of a 1 per cent solution of the chemical, a larger dose, such as 2.0 or 6.0 cc, unless the blood pressure falls too low, will induce

urticaria. Again, in such a case, the urticaria does not involve the recent former sites of wheals. When the dose of 10 cc of a 1 per cent solution was reached, the refractoriness was so decided that we could not break through it with larger doses, such as 20 cc, during an experimental period of eight or ten hours.

Effects on Permeability of Capillaries in Certain Areas If rose bengal is injected intravenously (2 cc of a 1 per cent solution), two or three minutes after the injection of the chemical—that is, at about the time the blood pressure starts to fall—the urticarial wheal assumes a pink tint. This result shows that this dye, which does not ordinarily stain the skin, filters from the capillaries along with fluid. This method is an excellent way for one to label the location of a crop of wheals. After the wheal is formed, it is not stained by an injection of the dye.

After the disappearance of the wheals, the injection of a second dose of the chemical will cause a flare or reddening of the rose bengal-tinted patches. As already indicated, whealing does not occur in these patches. This reddening is due to vasodilatation. This experiment shows that vasodilatation can occur at the site of a former wheal, but that the site is refractory to formation of edema. This reaction was observed many times.

Urticaria After Injection of the Chemical Into the Portal Vein Urticaria was as easily produced by making injections (1 cc of a 1 per cent solution) into the portal vein as by introducing the chemical into the femoral vein. Three experiments were performed. In these experiments the statements made previously relative to refractoriness and formation of a wheal were observed to apply. Thus it may be seen that the liver is not particularly efficient in removing the chemical.

Urticaria After Evisceration and Hepatectomy The blood pressure of eviscerated-hepatectomized dogs is so sensitive to the chemical that the usual urticaria-producing dose (1 cc of a 1 per cent solution) produced such a pronounced fall in blood pressure in a number of cases that urticaria could not develop. However, of nineteen experiments, decided urticaria was observed in six and slight to moderate urticaria in nine.

There was no good evidence indicating that absence of the liver sensitized the animals to the urticaria-producing substance, although it certainly sensitized them to the blood pressure-reducing action of the chemical.

Intra-Arterial Injection of the Chemical and Urticaria It was believed that the urticaria produced by an intravenous injection of the chemical was due to the local action of the chemical either on the endothelium of the capillaries in the skin or on the tissue cells after it had diffused from the capillaries. We believe this hypothesis to be more

likely than the view that the chemical acted on some constituent in the blood, which then acted on the capillaries or tissue cells. The results of the foregoing tests on hepatectomized animals showed that the urticaria-producing substance does not arise from the liver.

Accordingly, 0.3 cc. of a 1 per cent solution of the chemical in an isotonic solution of sodium chloride was injected into the artery supplying the lower legs and abdomen of 4 anesthetized dogs. In each instance, the flushing reaction and urticarial wheals developed only in the skin of the lower abdomen and legs. The carotid blood pressure, however, fell from 10 to 20 mm. of mercury in three to five minutes after the injection.

Two of these dogs, four hours after the first injection, were given 1 cc. of a 1 per cent solution into the femoral vein. The blood pressure fell 10 and 30 mm. of mercury, respectively, and a generalized urticaria appeared. However, the wheals did not appear in the old or former sites on the lower leg and abdomen, but in new sites and to a lesser extent than in the upper part of the body.

Production of Urticaria by the Intracutaneous Injection of the Chemical—This chemical is potent in producing an urticarial wheal with a peripheral flare when injected intracutaneously into a dog. From 0.02 to 0.04 cc. of a 1:1,000 dilution of the chemical in an isotonic solution of sodium chloride causes the production of a large wheal which cannot be distinguished from that caused by histamine. The total dose of sorbitol monolaurate was 0.02 to 0.04 mg.

The formation of the edema fluid is beautifully demonstrated when the intracutaneous injection is made while rose bengal is being injected intravenously.

Prophylaxis of Sorbitol Monolaurate Urticaria in the Dog—Heparin failed to prevent urticaria in five experiments. Epinephrine prevented the development of urticaria due to the chemical and hastens its disappearance. This fact was readily demonstrated in five experiments. Atropine in large doses up to from 4 to 6 mg., given in 1 mg. or 2 mg. doses intravenously, had no effect on the development or disappearance of urticaria in five experiments. Diphenhydramine hydrochloride was used to prevent the wheals in 9 anesthetized dogs and in 11 unanesthetized dogs. In the anesthetized dogs 50 to 100 mg. of diphenhydramine hydrochloride was given intravenously at least five minutes before the administration of the chemical. In only 1 of the 9 dogs were wheals produced, and in this dog they were small and few. It is of interest to note that the general flush of the skin and the flush which occurs in patches were not prevented. This observation indicates that the mechanism responsible for the flushing due to the chemical either is more resistant than the mechanism responsible for the development of a wheal or is different in nature.

In table 1 are shown the results for 11 unanesthetized dogs. It should be emphasized that in the case of these dogs the dose of the chemical was selected by experiment for each dog. Or, for example, if a dose of 1 cc of a 1 per cent solution caused complete collapse of the dog and urticaria did not occur because the blood pressure was too low, the dose was reduced. That is, if the appropriate dose was used, urticaria always occurred in our experience, and the development of the wheal

TABLE 1—Prevention of Monolaurate Urticaria in Dogs by Pretreatment with Diphenhydramine Hydrochloride (Benadryl Hydrochloride²)

Dog No	Wt, Lb	Sex	Diphenhydramine Hydrochloride*	Dose, Sorbitol, Mono laurate (Mg)	Signs and Symptoms						
					Itching	Flush	Redness in Patches	Wheals, Skin	Edema Mouth	Edema Eyelids	Weakness
1	12.5	F	Without	8	+++	---	+++	---	Edema	Edema	---
			With	10	---	+	---	None	None	None	---
2	15	M	Without	6	---	+++	---	---	Edema	Edema	++
			With	6	+	+	---	None	None	None	---
3	15	F	Without	6	None	+++	++	+++	Edema	Edema	None
			With	6	None	+	---	None	None	None	None
4	15	F	Without	10	+++	---	---	---	Edema	Edema	+++
			With	10	None	+	---	None	None	None	---
5	15	M	Without	9	None	---	---	+++	Edema	None	++
			With	9	None	None	None	None	None	None	+
6	19	M	Without	10	---	+++	---	+++	None	None	---
			With	10	+	+	---	None	None	None	None
7	13	F	Without	8	None	+++	---	+++	++	---	---
			With	8	None	+	+	None	None	None	None
8	12	F	Without	3	---	+++	---	---	+++	+++	+
			With	3	None	++	+++	---	---	++	None
9	13	F	Without	5	None	++	---	+++	+++	+++	++
			With	5	None	None	None	None	None	None	None
10	10	F	Without	2	+++	+++	+++	+++	++	++	++
			With	3	None	+++	+++	---	None	None	++
11	17	M	Without	9	---	++	+++	+++	+++	+++	None
			With	9	None	+	None	None	None	None	None

* The total dose was 50 mg, given intravenously. One or two days elapsed between each test on each dog. The sorbitol monolaurate was given five to ten minutes after the diphenhydramine hydrochloride.

was prevented by the appropriate dose of diphenhydramine hydrochloride.

It is entirely possible, however, that cases will be found in which wheal formation will not be entirely prevented. In this connection, it should be noted from the results in table 1 that, although edema or wheal formation was prevented in all dogs studied to date, itching and flushing were variably influenced.

On 5 other dogs we determined the appropriate urticaria-producing dose of sorbitol monolaurate (the interval between injections of this

compound was forty-eight to ninety-six hours) and injected tripele-
namine hydrochloride intravenously from fifteen to twenty minutes before
the given dose of the monolaurate

The amount of tripeleennamine hydrochloride used on the first 2 dogs
was 50 mg , but because it caused severe convulsions we decreased the
dose, even though the prevention of urticaria was not very definite in
1 of the 2 dogs receiving 50 mg

When we injected very slowly 4 mg per kilogram of body weight
of tripeleennamine hydrochloride in 2 of 3 dogs, neither edema nor
wheals developed and 1 of these 2 dogs and the third one (which had
wheals) had slight convulsions

ABLE 2—*Prevention of Monolaurate Urticaria in Dogs by Pretreatment with Tripeleennamine Hydrochloride (Pyribenzamine Hydrochloride®)*

Dog No	Wt, Lb	Sex	Tripeleennamine Hydrochloride	Dose, Sorbitol, Mono laurate (Mg)	Signs and Symptoms						
					Itching	Flush	Redness in Patches	Wheals, Skin	Edema Mouth	Edema Eyelid	Weak ness
1	19	M	Without	10	++++	++++	++++	++++	++-	++	None
			With (34 mg)	10	+±	++±	None	+±	+		
2	15	F	Without	5	+++	+++	++++	++++	++±	++±	+++
			With (50 mg)	5	None	+++	+++	+	None	None	++
3	17	M	Without	10	+++	++	++±	++	--	+	+
			With (31 mg)	10	None	None	None	None	None	None	None
4	18	F	Without	10	++±	++	++	+++	++	+	None
			With (32 mg)	10	None	None	None	None	None	None	None
5	19	M	Without	10	++++	+++	+++	+++	++-±	++++	++
			With (50 mg)	10	None	±	+	None	None	None	None

A METHOD OF ASSAY OF ANTIURTICARIAL DRUGS

The antiurticarial drugs which are now available—diphenhydramine
hydrochloride and tripeleennamine hydrochloride—are not so satisfactory
as might be desired Attempts undoubtedly are being made to produce
better synthetic compounds

Since urticaria can be consistently produced in dogs by the appropri-
ate dose of sorbitol monolaurate, this reaction would serve as the basis
of an assay for the antiurticarial properties of antihistaminic compounds

COMMENT

Clinical urticaria is considered an allergic phenomenon In the case
of sorbitol monolaurate one deals with a pure and relatively simple and
potent urticariogenic agent which causes a generalized urticaria when
introduced into the circulation of an animal naturally susceptible

The dog is susceptible, and the cat, rabbit and monkey are not
susceptible Man, as indicated by intradermal tests, does not appear

to be susceptible Sorbitol monolaurate is not unique in the property of producing a "triple response" on being injected intradermally, since many substances do this, nor is it in doing so when injected intra-arterially, since curare will do the same thing²² It is unique in being a pure, rather simple chemical substance which consistently produces a typical urticarial wheal when given intravenously in a dose of a few milligrams

Wheal formation in the skin is explained as being the result of a special form of cell injury in which histamine or an H substance is produced to cause a local increase in blood flow and capillary permeability If sorbitol monolaurate releases histamine to cause a wheal, why then does not histamine cause urticaria when given intravenously? It might be replied that when histamine is released in anaphylactic shock the blood pressure falls so low that whealing cannot occur, or that when histamine is given intravenously in a dose adequate to cause urticaria the fall in blood pressure is too great, or that when histamine is given slowly intravenously in amounts adequate to cause flushing of the skin and not cardiovascular collapse the concentration of histamine in the skin is not adequate to cause whealing On the other hand, sorbitol monolaurate is sufficiently injurious to the capillaries of the skin that sufficient histamine or H substance is released locally to cause urticarial wheals Such an explanation requires the additional assumption that when the drug is given in urticariogenic doses the skin is more susceptible than other tissues to injury with the monolaurate The evidence for this assumption is that in such doses no other anatomic lesions are observed nor are there any apparent physiologic disturbances

The results of the studies of refractoriness to the monolaurate-induced urticaria, as far as they have extended, show no difference between this urticaria in the dog and that induced by allergens or substances which apparently exhaust the ability of the cells to form an H substance in man The H substance released by the monolaurate has a histamine-like and thromboplastic action

SUMMARY

Knowledge regarding the mechanism of the urticarial reaction is outlined

The intravenous or intradermal injection of appropriate amounts of sorbitol monolaurate consistently causes urticaria in the dog, but not in the cat, the rabbit or the monkey The intravenous injection of 8 to 10 mg in a dog causes urticaria The intra-arterial injection of 0.3 cc of a 1 per cent solution causes urticaria in the skin confined to the

²² Grob D, Lilienthal, J L, and Harvey, D M Bull Johns Hopkins Hosp 80 299, 1927

distribution of the artery The intradermal injection of 0.02 to 0.04 cc of a 1:1,000 dilution in an isotonic solution of sodium chloride will cause the formation of a wheal with a surrounding flare in the dog, this reaction does not occur in man

By labeling the site of previous wheals by injecting a dye, rose bengal intravenously at the time wheals are forming, we showed that the site of a previous wheal is refractory to the formation of a new wheal for four to eighteen hours

A study of the refractoriness indicated that the urticarial reaction caused by the monolaurate resembles that caused by allergens

The evidence indicates that the intravenous injection of the monolaurate releases from the capillary endothelium or the skin in patches a substance or substances having a histamine-like and thromboplastic action

This monolaurate urticaria is ameliorated by diphenhydramine hydrochloride (benadryl hydrochloride®) and tripeleminamine hydrochloride (pyribenzamine hydrochloride®), the wheals being most readily prevented by these antihistaminic drugs

It is suggested that monolaurate urticaria in dogs may be used for the assay of antiurticariogenic drugs

COLLOID MILIUM

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SEVERAL recent reviews of the literature on colloid milium by Robinson and Tasker,¹ Reuter and Becker,² Way³ and others make it inappropriate to include a complete review in this report

Gilbert and Cox,⁴ both of the Australian Army Medical Corps, reported 8 cases of colloid degeneration observed at an Australian general hospital. They stated the belief that sunlight is an important factor in the etiology of this condition.

While the theory was expressed by Anderson,⁵ Way and others that a vitamin deficiency may exist and that it may be an etiologic factor in the development of colloid milium, there is not an unanimity of opinion as to the etiology of this condition. In the 2 patients whose cases I report here, the question of vitamin C as an etiologic factor is problematic. Both patients enjoyed good health, and their economic status was better than average.

Subjective symptoms were absent in both patients. The lesions were prevalent on the face, the ears, the sides of the neck and the dorsa of the hands. They were elevated and yellowish red and varied from 1 to 5 mm in diameter. In some areas the lesions were discrete, while in others they were closely packed together. They were firm and had the feel of lesions of lymphangioma circumscriptum. Puncture of a lesion usually elicited a minute amount of blood.

It was readily seen that the lesions were not true vesicles. Pressure was necessary to empty the contents of the "pseudovesicle" or "bulla." The "pseudobulla" was apparently the result of the confluence of several lesions. The contents of a lesion were granular and gelatinous.

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1 Robinson, S. S., and Tasker, S. Colloid Degeneration of the Skin, *Arch Dermat & Syph*, **52** 180-181 (Sept) 1945

2 Reuter, M. J., and Becker, S. W. Colloid Degeneration (Collagen Degeneration) of the Skin, *Arch Dermat & Syph* **46** 695-704 (Nov) 1942

3 Way, S. C. Colloid Milium. A Vitamin Deficiency Disease? *Arch Dermat & Syph* **45** 1148-1155 (June) 1942

4 Gilbert, T. M., and Cox, C. B. Colloid Degeneration of the Skin. Report of Eight Cases, *M. J. Australia* **2** 21 (July 6) 1946

5 Anderson, N. P., cited by Way³

Benign cystic epithelioma, hydrocystoma and lymphangioma circumscriptum are the conditions most likely to be confused with colloid milium

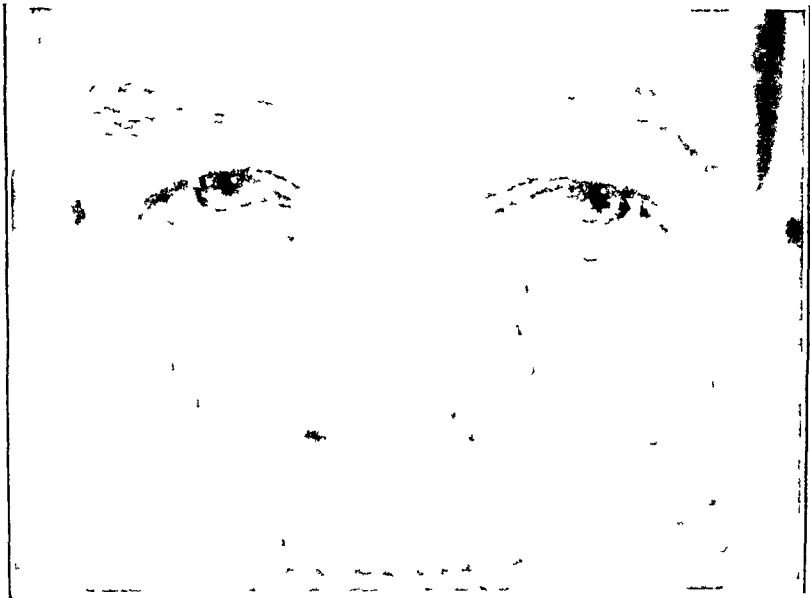


Fig 1 (case 1) —Appearance of lesions on the face

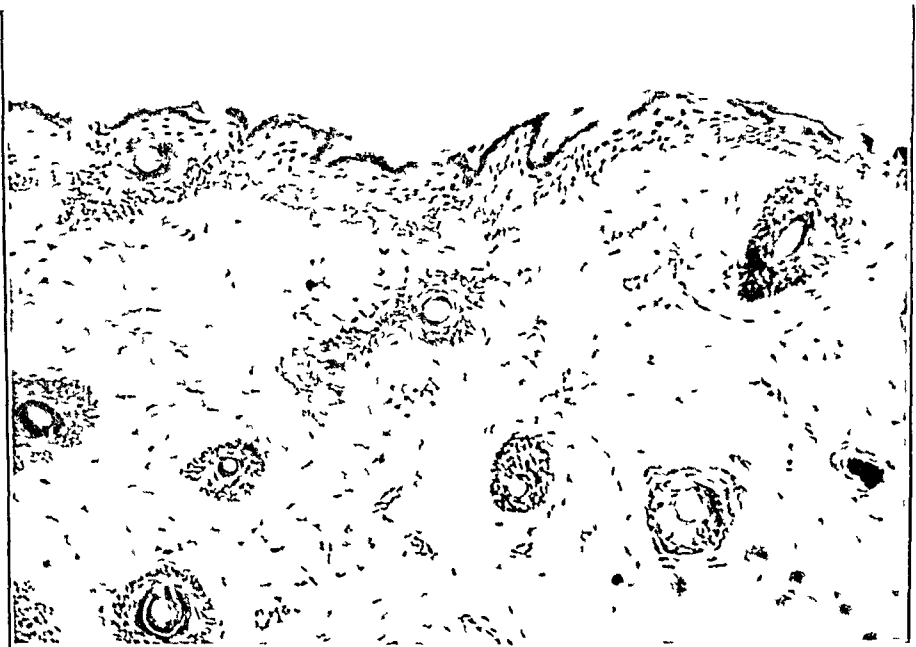


Fig 2 (case 1) —Section of a lesion, hematoxylin and eosin stain, $\times 75$

REPORT OF CASES

CASE 1—T J M, a white man aged 39, was first seen by me in December 1946. His occupation was manager of a trucking business, and he estimated that he worked out of doors 50 per cent of his time. His general health was excellent.

He had red hair, brown eyes and a ruddy complexion. His face, ears and the dorsa of the hands presented lesions as previously described, which had begun at the age of 30. Various treatments, including local keratolytic remedies, roentgen irradiation and curettage of small areas, were carried out. Only those areas which were curetted remained free of lesions. On Oct 30, 1947, treatment was begun with ascorbic acid, 50 mg three times a day. The patient was last seen by me on March 23, 1948. After five months of medication with ascorbic acid, the condition appeared to have been uninfluenced. The patient said, "Doctor, I can recall that this condition was much worse four or five years ago, and it is worse every summer and gets better in the wintertime"

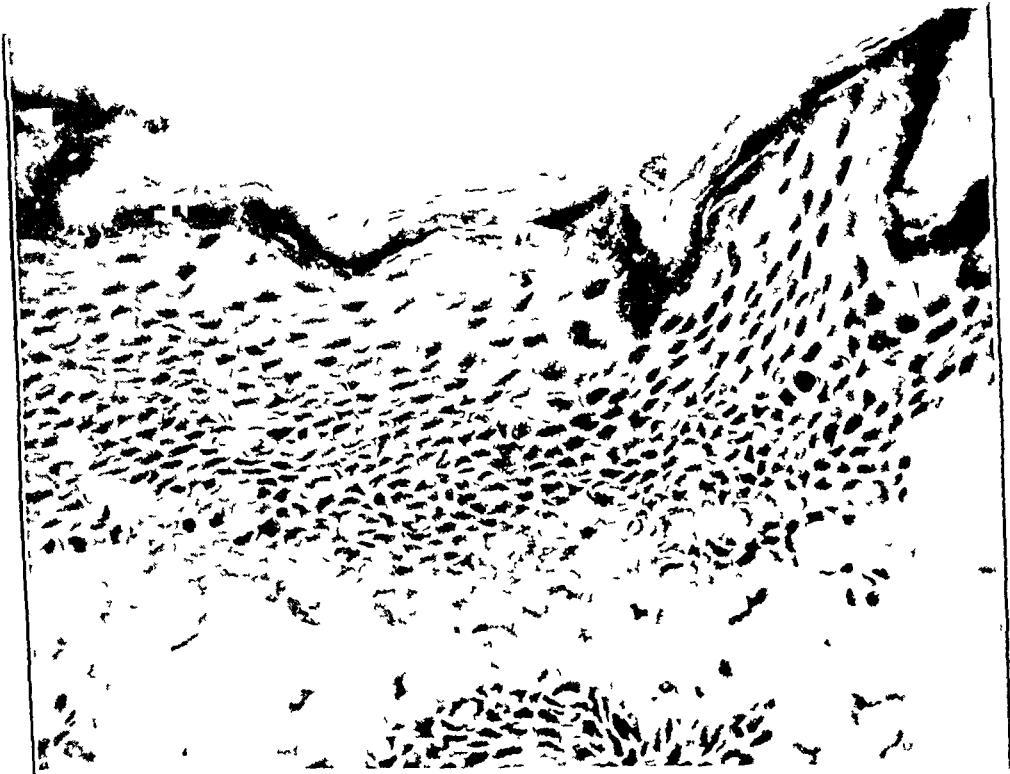


Fig 3 (case 1) —Section of a lesion, hematoxylin and eosin stain, $\times 350$

CASE 2—A C, a white man aged 40, was first seen by me on Aug 30, 1945. He operated a farm equipment agency and spent about half his daylight time out of doors. His general health was excellent. His eyes were hazel colored, and he had a ruddy complexion. On his face, the sides of the nose, the ear lobes, the back of the neck and the dorsa of the hands were a large number of elevated, yellowish red lesions, as before described. The patient was seen from Aug 30, 1945, to Dec 7, 1946, at fairly regular intervals. The maximum safe dosage of roentgen radiation was administered, without noticeable results. Curettage of areas of the dorsa of the hands produced corresponding smooth atrophic areas. This result apparently displeased the patient. Subsequently, solicitation by mail failed to obtain the patient's cooperation in testing the value of ascorbic acid in treatment of his condition.

HISTOLOGIC EXAMINATION

The reports by different histopathologists vary in lesser details, but the essential facts are in agreement. The epidermis is thinner than

normal, the rete pegs are absent, and homogeneous masses which represent the degenerative process are found in the upper portion of the derma. There is a tendency for the masses to appear at right angles to the epidermis. The degenerative process affects the walls of the blood vessels.

TREATMENT

Curettage followed by keratolytic dressings brought about the most satisfactory destruction of the lesions. Roentgen therapy was valueless in both of my patients. Treatment with ascorbic acid for approximately five months failed to improve the lesions in 1 patient. Probably protective measures against sunlight offer the best treatment against this condition.

SUMMARY AND CONCLUSIONS

Two cases of colloid milium of Wagner are reported.

The disease is probably not as rare as has been previously believed.

In those few cases reported in which administration of ascorbic acid cured the condition or influenced it favorably, the question of coincidence is in order.

The patient in this report who cooperated in experiments with prolonged ascorbic acid medication failed to show improvement. He had noted that the condition improved and regressed without apparent cause, except that he observed that it was worse in the summer.

Geographic location of patients whose cases have been reported appears to influence the incidence of the disease. Where the daily average of hours of sunlight is greatest it seems that this condition is more prevalent.

Results of treatment are unsatisfactory.

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ABSTRACT OF DISCUSSION

DR NELSON PAUL ANDERSON, Los Angeles. I am sure that you could not expect anybody from a citrus fruit-growing state to agree with Dr. Hailey's remark concerning the lack of value of ascorbic acid in treatment of this disorder. I believe that everyone has certain preconceived ideas, particularly as regards degenerative diseases. A slide like the one shown today immediately suggests an irreversible change. However, many of these degenerative changes are not irreversible. The answers may not be known now, but the lock is there waiting to be opened by the right key. Whatever the causative factors may be in this disease and in other so-called degenerative diseases, if we take the viewpoint that these are irreversible degenerative diseases about which nothing can be done, then we will not be on the lookout for new therapeutic ideas which might be of benefit. I would like to point out that this was the situation in Way's case in which there was a return of the skin to normal, and in Robinson's case, in which there was also a return to a normal condition. Along this same

line of thought there is the presentation of Burgess, of a case of necrobiosis diabetorum in which there was a return to normal. In lichen sclerosis et atrophicus I have seen astounding reverses to normal with the local application of estrogenic cream in women who had several hundred lesions scattered all over the body and genitalia. One positive result in a disease where all previous attempts have been negative is worth a great deal more than all the negative results that are obtained. I have little doubt as to the value of ascorbic acid in treatment of colloid degeneration of the skin. Even with the daily administration of 500 cc of ascorbic acid by mouth, Robinson could raise the blood level only to 0.8 mg per hundred cubic centimeters. Improvement was noted two months after the beginning of this therapy. The fact that people are in certain so-called higher economic groups means nothing in regard to adequacy of diet. Finally, I should like to mention that, in a number of cases of colloid degeneration, hypercholesteremia occurs. This condition might be the result of an effect of the adrenal gland on the thyroid gland.

DR. JOHN BELISARIO, Sydney, Australia. I was interested to hear Dr. Hailey's paper and Dr. Anderson's discussion. Although this disease is rare, in Australia it is seen every now and again. Furthermore, I would like to mention that this condition is more frequent in fair-skinned blonds who are out in the sunlight a good deal. I saw more of it in New Guinea than is usual in Australia. The reason is probably that the people in New Guinea had their hands exposed to strong sunlight all day. With regard to treatment, I have not been successful with the use of ascorbic acid. I have used it in large doses but have seen no improvement. Some of my colleagues told me that they had seen improvement under this treatment. I have seen 1 or 2 cases clear up independently. I have used roentgen irradiation but the only thing that has given complete regression has been electrodesiccation or curettage.

DR. HAILEY, Atlanta, Ga. I wish to thank Drs. Anderson and Belisario for their discussions. I was especially interested in hearing Dr. Belisario state that colloid milium was not a common condition but was more frequent in some geographic areas than others.

Colored pictures were made before the treatment with ascorbic acid and after treatment. Through the use of a hand lens I was unable to note any diminution in the number of lesions.

CALCIFEROL IN THE TREATMENT OF CUTANEOUS TUBERCULOSIS

HENRY E MICHELSON, M D

With the Collaboration of John R Haserick, M D

MINNEAPOLIS

VITAMIN D therapy has been used in cutaneous tuberculosis by a large number of clinicians in many countries since the first reports of Charpy and Dowling extolled the value of calciferol (vitamin D₂) in the treatment of lupus vulgaris. That the method has real value is proved beyond a doubt, but there are still some unanswered questions about the action and use of this potent vitamin, therefore, a review of our experience and of that of others up to the present time seems in order.

In using calciferol in the treatment of cutaneous tuberculosis at the University of Minnesota Hospitals, the French and English methods of administration have been combined. We prefer Dowling and Thomas' adjustment of daily doses to each patient. Our rule has been to give, orally, 1,000 units per kilogram of body weight per day to the bedridden patient and up to 2,000 units per kilogram to the ambulatory patient. It is interesting to note that despite this attempt to prevent reactions by halving the dose for bedridden patients, they were the very patients who had the largest number of toxic reactions.

Charpy recommended and has continued, to the time of writing, to prefer alcohol as the vehicle for the crystallized vitamin D₂. He stated the belief that calciferol in oil did not give consistent results. Mayoux stated that vitamin D in oil was consistently ineffective. Charpy¹ stated recently that when no improvement occurs by the fifteenth day of administration, failure of absorption or failure of tissue permeability owing to the presence of too much salt in the tissues must be suspected. He did not state how the presence of these conditions could be established.

At first viosterol in oil was used, because it was available, later a solution of calciferol in propylene glycol (drisdol®),² especially

From the Division of Dermatology, University of Minnesota, Henry E Michelson, Director

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948

1 Charpy, M. J. Vitamin D in Cutaneous Tuberculosis, *Lancet* 2 398, 1947

2 The drisdol® used in this study was furnished by the Winthrop Chemical Company

prepared in a concentrated form of 50,000 units per cubic centimeter, was used. The results varied with either solvent, and we cannot state that either is superior or that fewer reactions are encountered with the one or the other. The advantage of propylene glycol as a solvent is that, being water miscible, it is injectable. This property is being utilized in inhalation experiments now under way in cases of pulmonary tuberculosis, when the substance is vaporized, it can be utilized without danger of lipid pneumonia.

We have now treated 25 patients with cutaneous tuberculosis with calciferol. The series comprises 7 patients with lupus vulgaris, 9 with erythema induratum, 4 with papulonecrotic tuberculids and 5 with colliquative tuberculosis.

LUPUS VULGARIS

Since the results of treatment with calciferol are especially striking and successful in lupus vulgaris, one must analyze this particular form of tuberculosis in order to find, if possible, an explanation for the curative susceptibility of the disorder to large doses of the vitamin.

The disease has a definite geographic distribution outside the United States, although occasional patients with lupus vulgaris are seen here, most of them are not native born but come from areas where the disease is endemic. In addition, patients with lupus vulgaris come from a stratum of society which often means restricted purchasing power and, hence, an inadequate diet, frequently with severe deficiency of the foods that contain vitamin D, there has been prenatal deprivation, both calorically and in vitamin content. Neumann has stated that in pulmonary tuberculosis, a normal daily diet of 40 calories per kilogram of body weight was desirable, with an acceptable mixture of foods, this standard is rarely encountered in those areas of Western Europe where lupus vulgaris is so common. The relation of vitamin D to sunlight is well known, the studies of Marchionini³ demonstrated the absence of lupus vulgaris in those parts of the world where the number of days per year with bright sunlight is high.

Although nutrition and climate both play a prominent role in susceptibility to lupus vulgaris, climate seems the more important. The incidence of lupus vulgaris in different climates shows that moist, cool areas, poor in sunlight, favor development of the disease. In Europe it is much more frequent in the north than it is near the Mediterranean. In fact, the incidence declines from north to south, and the disease is practically nonexistent near the Equator. Marchionini cites many well known observers on this point, for example, Pautrier's patients in Strasbourg came largely from the valleys of

³ Marchionini, A. Die Hauttuberkulose in Anatolien, Arch f Dermat u Syph **185** 363, 1944.

the Vosges, a relatively moist and cool region. In Germany, Stumpke called attention to the great number of patients from the western and southwestern areas near Switzerland (where Miescher had noted that his patients came largely from the peasant class) and emphasized the poor economic level as well as the scarcity of sunlight in the areas of the country where lupus was most frequent. Gron reported that 60 cases of lupus vulgaris had been reported in Bergen, as against 18 for the same period in Stockholm. It is interesting to note that in northern Italy, cutaneous tuberculosis accounts for 6.75 per cent of all cases of cutaneous diseases, whereas in Rome, the percentage drops to 1.07 and in Naples, to 0.8. The only figures available to us for the United States were furnished by Buckley, by Duhring and by Pusey. All three investigators stated individually that the incidence of lupus vulgaris in the dermatologic clinics where they tabulated reports of cutaneous diseases was 0.3 per cent.

Incidence of Cutaneous Tuberculosis in Relation to all Cutaneous Diseases

	Oslo (Danbolt), %	United States (Spitzer), %	Ankara (Marchionini), %
Cutaneous tuberculosis, Total	3.76	0.818	0.53
Tuberculosis luposa	1.5	0.3	0.18
Tuberculosis colligativa	0.45	0.2	0.34
Tuberculosis indurativa	0.41	0.01	0.002
Tuberculosis ulcerosa	0.45		0.004
Tuberculosis verrucosa	0.06	0.3	0.002
Tuberculosis papulonecrotica	0.019		
Tuberculosis lichenoides		0.008	

Marchionini studied tuberculosis of the skin in Turkey, where, in contrast to western Europe, the total number of cases of cutaneous tuberculosis was only 0.53 per cent and that of lupus vulgaris only 0.18 per cent of all recorded cases of cutaneous disease. An interesting comparison of the frequency of various types of cutaneous tuberculosis in northern Europe and in the United States with the frequency of the same types in Turkey is afforded by the table.

The striking contrast occurs in the frequency of lupus. Obviously Danbolt's and Marchionini's figures are more reliable, for they were taken from their own clinics in one locality, whereas Spitzer's were calculated from the meager American statistics available. The total percentage of lupus in Oslo is much greater than that in either the United States or Ankara, and the percentage in Ankara is much the lowest of the three figures quoted.

Without delving further into the geographic and climatic factors that favor the development of lupus vulgaris, one may readily conclude that sunlight must play a decided role, but there are some exceptions which turn one's attention to diet. Trubitsch found no lupus vulgaris in the Eskimos of western Greenland, while Olin found the percentage in Finland to be about the same as in other parts of western Europe,

in spite of the high mortality rate for pulmonary tuberculosis in Finland, these data may be contrasted with those for Japan, where the incidence of pulmonary tuberculosis is also extremely high but, where there is practically no lupus vulgaris. In China, Richter found cutaneous tuberculosis to be less frequent than in northern Europe, but present to an appreciable degree. One must therefore investigate, if possible, the social, environmental and nutritional factors, a procedure which offers many difficulties.

Von Mallinckrodt-Haupt called attention to the unhygienic environment of patients with lupus vulgaris in the Eifel district of Germany, their general poverty, their dwellings with dark, unventilated rooms, their lack of bathing facilities, and their diet of potatoes and cereals, low in vitamins. These factors combined with the small number of hours of sunlight per year, make for conditions which we consider favorable for the development of lupus vulgaris, particularly when one keeps in mind the ever present infective sources both human and bovine in backward areas. Although these factors do not entirely explain all lupus vulgaris cases, a sun-poor, cold climate, together with an inadequate diet, seems to dispose to the development of lupus vulgaris much more than does an inadequate diet in a sunny warm climate.

Surely patients with such a disease are fit subjects for a therapeutic regimen which includes improved general nutrition, possibly vitamin D in massive doses in some way rectifies the main deficiency or repairs damage done when the patient was under less favorable dietetic influences.

Before the advent of vitamin D therapy in lupus vulgaris the most successful treatment of that disease was the Finsen form of ultraviolet therapy. According to Lomholt, this form of treatment, combined with a general antituberculosis regimen, gave promise of about 80 per cent success especially when begun at the first appearance of the disease. Just as today one may ask why vitamin D brings about improvement in cases of lupus vulgaris, so did the advocates of the Finsen treatment try to find the reason for its beneficial action. Obviously the first thought concerned the effect on the tubercle bacillus, but it was soon demonstrated that the chemical rays of the Finsen light penetrated to only about 0.1 mm and below this were entirely lost so bactericidal action could not have been the reason for the healing action. Most observers finally came to the conclusion that since healing under Finsen treatment brought about scarring, what actually took place was the production of an intense tissue reaction. This process began with an active hyperemia, with dilatation and thrombosis of the superficial and even of deeper vessels, and was followed with edema and cellular infiltration, resulting in vacuolation and necrosis of the epithelium and often in necrosis of the lupous

tissue, with crusting and subsequent formation of fibrous tissue. Healing often was incomplete, areas of lupous tissue found in the scar had to be dealt with. It was noticed that patients who lived at Finsen institutes made more progress than those who lived at home and only attended for irradiation. When the Gerson salt-free diet was introduced, it was also observed that the Gerson diet plus the Finsen treatment was superior to either alone.

Throughout the history of successful therapy for lupus, nutritional and hygienic factors have played an important part. Now the success of vitamin therapy seems to throw some light on the reason. Vitamin D is produced and found in the skin. Ultraviolet radiation is important in the production of vitamin D. The lupus vulgaris patient must have, or lack, certain qualities of the tissues which make him susceptible to this form of tuberculous inflammation. Evidently, when his skin becomes suffused with vitamin D, a reaction takes place similar to that produced by the Finsen treatment. Healing is apparently brought about in the same manner in both forms of treatment. It seems fair to presume that there is a common factor, and that Finsen therapy was probably successful because of the local production of vitamin D. The interrelation of the various* vitamins is well known, hence a diet rich in several vitamins may have assisted such action in Finsen therapy. The reports of combined Finsen and vitamin D therapy are very good, but much time and observation are needed in order to evaluate any procedure in so resistant, chronic and recurrent a disease as lupus vulgaris.

Charpy, Dowling, Lomholt and others are in accord about dosage, duration of treatment, percentage of improvement and other factors in the treatment of lupus vulgaris. They agree that most patients tolerate large doses of vitamin D and that the best effects are produced at almost a level of overdosage. Dowling stated that the total dose in his cases ranged from 9,500,000 to 62,500,000 units in adults and from 4,500,000 to 33,500,000 units in children. These writers also agree that the treatment must be carried on at reduced dosage for as long as a year. In successful cases there is no doubt about clinical cure, the anatomic cure is doubtful.

In ascertaining the value of treatment with calciferol in lupus vulgaris, in addition to our own observations, we have carefully examined the literature which has accumulated over the past five years and have been fortunate in receiving valuable personal communications from Dr. D. E. Macrae of England and Dr. G. Miescher of Switzerland. The experiences of almost all those who have worked with calciferol are much alike. There are some small variations, but the general uniformity of the results speaks for the success of the method.

It may be stated unequivocally that calciferol is of great value in the treatment of lupus vulgaris. It is not a specific, but it acts more

favorably in lupus vulgaris than in any other form of cutaneous tuberculosis in which it has been tried. The importance of familiarity with the rate of progress of the disease, variation in dosage with the vitamin, combination of the treatment with physical therapy, the all important time element, and many other details can be appreciated only when they are dealt with. Regulation of the dose to suit the patient must be emphasized. Although 100,000 to 150,000 units per day (1,000 to 2,000 units per kilogram of body weight) is the usual dose employed, we have found it advantageous to reduce the dose to as low as 10,000 units daily for the patient who is somewhat intolerant of calciferol.

Progress under calciferol therapy is by no means uniform in all cases. There is a decided variation, both in the time required for response and in the rate of improvement. There may be an initial period of lack of response, or even of increase in the inflammatory appearance, but if the dose is made tolerable and the treatment persevered in, improvement is indicated by a flattening of the plaques, a dulling of the color and, soon, the appearance of white areas between the lupous tissues. Gradually, these areas, which are composed of scars, increase, and fewer and fewer lupous nodules can be seen. Complete clinical scarring may result, but in our series we have not as yet encountered a case in which we were confident from the macroscopic appearance that there was no pathologic activity left.

Microscopic examination of treated areas has revealed tuberculoid structure. In an instance of slow healing a change in the type of structure found was in accord with an observation of Miescher's, that results of histologic examinations made within a few months after the beginning of treatment indicated a tendency for the frank tuberculoid structure to change to a sarcoidal one. This variation may be significant and may even throw some light on the etiology of sarcoidosis, but it cannot be discussed here. All observers have been dismayed at the presence of traces of tuberculous tissue in the areas which apparently were completely healed under calciferol treatment.

In America, one does not often encounter a patient with the severe, destructive and ulcerating lesions seen in Europe, hence, we cannot state which forms of lupus respond best to calciferol therapy. Macrae has tabulated his impressions in that regard. It is our conviction, however, that the more severe and extensive the disease, the longer the treatment must be carried out, and that sustained treatment, even though the dose is much reduced, is better than stopping the treatment completely and then starting it again.

We have not encountered any effects on pulmonary lesions, the presence of which had been determined historically or roentgenologically, nor have we seen the production of pulmonary lesions not previously suspected. The latter result has, however, been reported and

must be kept in mind. Not only pulmonary tuberculosis but also renal tuberculosis has become manifest or developed during calciferol therapy.

A combination of treatment with various physical devices, such as the Kromayer lamp or the Finsen light, or of cautery or application of chemical pastes, with administration of calciferol is entirely feasible and beneficial but fortunately is not often needed. Injections of streptomycin combined with or interspersed with administration of calciferol are indicated, we believe, in a case in which the lesions are resistant or in which progress has come to a standstill. Our experience with such a case is limited to a single instance, in which healing was not at all satisfactory until streptomycin was added, then scarring began and progressed favorably. For this patient the dose of calciferol was reduced to 25,000 units daily, because of some signs of intolerance. Our experience is too small to advise reducing the dose of calciferol when giving streptomycin, but it is a point worthy of consideration.

The addition of calcium is now considered unnecessary when patients are ingesting an average diet. Only those patients deprived of calcium-containing foods need supplemental calcium.

OTHER DISEASES

Papulonecrotic Tuberculid—One case of papulonecrotic tuberculid of the face responded well in two weeks' time, but after six weeks of therapy the serum calcium rose to 15 mg per hundred cubic centimeters and the calciferol was discontinued. There was no recurrence of the disease in several months. On the other hand, treatment with calciferol produced no change in the condition of a woman of 24 with papulonecrotic tuberculid, even after five months of treatment. It is of interest that in this case the amount of calcium in the serum and urine was within the normal range after four months of treatment. A patient with extensive papulonecrotic tuberculid involving both legs and arms had had the lesions for six years. There were recurrences and increasingly severe involvement each winter. Under continued calciferol treatment the number of lesions decreased and the seasonal exacerbations were lessened, but lesions still persisted.

Vitamin D therapy in our few cases of papulonecrotic tuberculid has not been successful. In so-called rosacea-like tuberculid we also have seen no striking effect.

Tuberculous Adenitis—Calciferol was used in 5 cases of tuberculous adenitis, including 1 of colliquative tuberculosis. No local change was noted in 3. In the other 2, a severe local reaction occurred, consisting of pain, swelling, fluctuation and drainage of the glands during the second week of treatment. Addison's disease developed in 1 of the latter patients while he was being given calciferol. The second patient improved after the initial softening and drainage of the nodes,

she herself requested that therapy be resumed because of a feeling of well-being she had while taking calciferol

Macrae, of the Morland Clinics, in England, wrote one of us (H E M) that he has administered vitamin D in from 30 to 40 cases of tuberculous adenitis. He noted a flare-up, similar to the Herxheimer reaction, especially in children, however, after a month or six weeks of increased swelling with breaking down and pus formation, or with increased discharge from sinuses, noticeable improvement took place

The benefits of calciferol have shown themselves strongly in several ways. Firstly, in the acute flare-up nodes hitherto unsuspected have sometimes shown themselves, so that more complete eradication of the disease can be carried out. I feel it is these small nodes, containing a few tubercle bacilli and not spotted in the ordinary course of events, that lead to a recurrence of the trouble months or even years afterward.

Operation is surprisingly easy compared with the difficulties of the old days. The most striking feature has been the disappearance of matting and periadenitis. The nodes can be firmly gripped without their bursting and discharging tuberculous pus in the wound, and I have found that after periods of treatment varying from two to nine months, the nodes resemble sebaceous cysts in the ease with which they can be removed.

Roentgenograms of the neck have shown a considerable increase in calcification, and sections of the lymph nodes after removal have shown a very large proportion of calcium deposits, particularly in the center of the node, in some, no lymph node can be seen. In others, a small rim of tuberculous tissue has been found at the periphery. I feel surgical operation is still an essential part of the treatment.

Dr Macrae unhesitatingly states that calciferol is of very great help, and that although it cannot be regarded as curative, treatment is speeded up and results are pleasing in tuberculous adenitis. As has been stated, our experience is not large. In 1 case, after progress had come to a standstill with calciferol, streptomycin was given, rather striking improvement, scarring and arrest (perhaps cure) of the process resulted.

Erythema Induratum Erythema induratum has not been affected remarkably under calciferol therapy. We believe that the patient should be given the benefit of a three months' trial. If no improvement has taken place in that period, it is doubtful whether further benefit can be expected. Since circulatory factors are important in erythema induratum, the ideal trial should be combined with bed rest. Under such a regimen we had fair success in 1 case, but as soon as the patient became ambulatory the lesions recurred.

TOXIC REACTIONS

In our experience, the systemic toxic symptoms and signs were minimal in the group of 25 ambulatory patients. As a precautionary measure, calciferol was not administered to any patient with arteriosclerosis or with impaired renal function. When toxicity occurred, the earliest sign was nausea, with anorexia and headache the next

most frequent. In no case in which the patient was ambulatory was it necessary to stop administration of the drug because of toxic symptoms, though a rapid onset of hypercalcemia (the level for serum calcium was 15 mg per hundred cubic centimeters) in 1 case prompted us to withdraw it.

Of the 8 bedridden patients, 5 had reactions considered severe enough to discontinue the drug, in spite of reduction (for 4 of them) to one-half the amount of calciferol per kilogram given to the ambulatory patients. Abdominal pain was severe in 2 patients. There was no adequate explanation for the pain except the one favored particularly in England that vitamin D liberates lead from the bones and, when the mobilization is rapid, produces the nausea, vomiting and abdominal pain of lead poisoning. Examination of the excretions for lead was not carried out in any of our cases.

Even after the drug was discontinued hypercalcemia and toxic symptoms persisted for two months in 3 of the 5 bedridden patients. In our experience toxic symptoms did not develop in any patient without hypercalcemia, though hypercalcemia developed in several without toxicity.

Though we had expected systemic toxic reactions to massive doses of calciferol, we were unprepared for the severe local Herxheimer-like reactions in tuberculous adenitis. These usually occurred during the second or third week of therapy and consisted of increased redness, pain and softening of the lymph nodes with copious drainage, and of increase in the area of involvement. When observed over a longer period of time the local reaction usually subsided and continued improvement then seemed to begin.

In the case of tuberculous adenitis in which Addison's disease developed with crisis during the second week of calciferol treatment, it is noteworthy that a severe local reaction took place at the site of the subcutaneous adenitis followed with fluctuation and drainage. It is plausible to assume that a similar local reaction may have occurred in the adrenal glands, resulting in the crisis of Addison's disease.

MODE OF ACTION

There has been no satisfactory explanation for the success of calciferol in the treatment of lupus vulgaris. A hypothesis based on the well known effects of vitamin D does not adequately explain either the clinical response or the pathologic findings. Nevertheless several factors involved are applicable to physiology and pathology of the skin.

Effect of Vitamin D on Mineral Metabolism—The theory first suggested to explain the effect of calciferol in lupus vulgaris was the natural one that healing was related to the hypercalcemia produced by calciferol. However both Charpy and Dowling reported patients who responded well with no change in the serum calcium while other

patients with hypercalcemia did not show a clinical response. Moreover, in post-treatment biopsy in Charpy's cases studied by Vachon and Feroldi,⁴ as well as in those of our own small series, there was no evidence of deposition of calcium in or around the tuberculous tissue.

In our cases high blood calcium was a common finding, the level often reaching 16 mg per hundred cubic centimeters. The rise usually was preceded by an increase of calcium in the urine, the level of which rose from a normal quantitative value (Sulkowitch test) of below 100 mg per hundred cubic centimeters to as high as 800 mg per hundred cubic centimeters. It was noted that acidity of the urine was necessary to maintain a direct relation between the level of serum calcium and that of urinary calcium. For 1 dehydrated patient with alkaline urine, the quantitative value (Sulkowitch test) was 89 mg per hundred cubic centimeters, while the serum calcium persisted at 15 mg per hundred cubic centimeters after calciferol was discontinued. With restoration of the fluid balance to normal and acidification of the urine with nitrohydrochloric acid, the urinary calcium excretion rose to 878 mg per hundred cubic centimeters, followed with a rapid drop in the serum calcium.

No change in the serum phosphorus was noted after administration of calciferol. However, the alkaline phosphatase rose late in 3 cases, from normal pretreatment values of 22, 18 and 14 King-Armstrong units to 46, 22 and 18 King-Armstrong units, respectively. In each case, the value returned to normal after the drug was discontinued. These data are in contradistinction to the unchanged or decreased phosphatase values reported by Reed when massive doses of vitamin D were given to arthritic persons, and to the severe decrease in serum phosphatase observed by Hansen, McQuarrie and Zigler in 4 cases of osteogenesis imperfecta in which values for blood phosphatase had been normal before treatment. At best, however, the changes in the level of phosphatase would seem to be a secondary factor, they are difficult to correlate with the therapeutic results in cutaneous tuberculosis.

Direct Effect on the Tubercle Bacillus Attempts to determine the bactericidal action of vitamin D have resulted in contradictory findings. Steenken and Baldwin,⁵ in 1937, found no in vitro evidence of a bactericidal effect on cultures of the tubercle bacillus. On the other hand, in 1946, Raab⁶ reported that a complete absence of growth of tubercle

⁴ Vachon, R, and Feroldi, J. Le traitement du lupus tuberculeux par la methode de Charpy. Les resultats anatomiques, Ann de dermat et syph **5** 241, 1945.

⁵ Steenken, W, and Baldwin, E. R. The Effect of Irradiated Milk Compared with Vitamin D Oils on Inhalation Tuberculosis of Guinea Pigs, Proc Soc Exper Biol & Med **37** 348, 1937.

⁶ Raab, W. Vitamin D—Its Bactericidal Action, Dis of Chest **12** 409, 1946.

bacilli had resulted when calciferol was given in propylene glycol, but that no change had occurred when propylene glycol alone was given. Dr. Robert Patnode,⁷ of the Department of Bacteriology, University of Minnesota, repeated these important experiments but found that the calciferol in propylene glycol had no more bactericidal effect than did the propylene glycol, which he used as a control.

Most authorities who support the theory of direct action on the bacillus call attention to the local reaction, which has frequently been noted soon after treatment was started. It has been likened to the Herxheimer reaction after antisyphilitic treatment and seems to be limited to cutaneous tuberculosis among all the diseases treated with vitamin D. It was the most common reaction in our cases of tuberculous adenitis and colliquative tuberculosis and was often severe enough to necessitate discontinuing the treatment. Miescher stated that tubercle bacilli could still be identified in the secretion from the lesions of a patient with colliquative tuberculosis, who had been under treatment with vitamin D for over one year.

Calorigenic Effect of Vitamin D Seel⁸ observed that the basal metabolic rate was lowered in rickets, and that vitamin D restored it to normal. Reed,⁸ in 1934, found that the drug produced an increased calorigenic effect when given in subtoxic doses to normal rats. Steck, Miller and Reed⁹ found that "para-thor-mone" had no calorigenic effect. This information led to experiments on dogs by Deutsch, Reed and Struck,¹⁰ who found that vitamin D no longer had its calorigenic action after thyroidectomy. Bartoli, Feldman and Barnes⁸ removed the pituitary gland from dogs and still found no calorigenic response to vitamin D. Thus it would seem that the preparation exercises a calorigenic effect, but mainly through the thyrotropic control of the anterior pituitary gland.

The relation between tissue oxygen consumption and vitamin D intake was studied by two investigators. Presnall,¹¹ in 1937, found that the "oxygen uptake of the skins of rats on a vitamin D-deficient

7 Patnode, R. Personal communication to the author.

8 Cited by Reed, C. I., Struck, H. C., and Steck, I. E. *Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations*, Chicago University Monographs in Medicine, Chicago, University of Chicago Press, 1939.

9 Steck, I. E., Miller, D. C., and Reed, C. I. The Effect of Parathormone on Basal Metabolism of Normal Dogs, *Am J Physiol* **110** 1, 1934.

10 Deutsch, H., Reed, C. I., and Struck, H. C. The Rôle of the Thyroid in the Calorigenic Action of Vitamin D, *Am J Physiol* **117** 1, 1936.

11 Presnall, A. K. The Relation of Vitamin D to Skin Respiration, *J Biol Chem* **121** 5, 1937.

diet was only 50-70 per cent of control rats. Gelfan,¹² in 1935 studied the effect of viosterol on frog muscle. He found that the vitamin D increased the mean oxygen consumption as much as 29 per cent over that of normal controls, which was "analogous to the increased respiration of tissue from thyroid-treated animals."

Clinically hyperthyroidism frequently is associated with a negative calcium balance and occasionally results in osteoporosis. Both vitamin D and 'para-thor-mone' have been found to correct this negative balance but what the clinical relation is between hyperthyroidism or hypothyroidism and lupus vulgaris or other forms of cutaneous tuberculosis is not clear. It is noteworthy that Feeny and his associates¹³ recently reported a case of "moderate hyperthyroidism" in which the patient had had lupus vulgaris for twenty years, and in which it did not respond after five months of treatment with calciferol. Thus there are three possible bases for the action of calciferol in cutaneous tuberculosis: the hypercalcemia, the direct effect on the bacillus and the improved metabolism, none of which seems adequate in itself. Since the histologic change in tissue in the lesions of lupus vulgaris after treatment with calciferol is mainly an increase in fibrous tissue and not a deposition of calcium, the action of the vitamin would seem to be due more to an improvement in tissue metabolism than to a change in the mineral constituents. A direct effect on the bacillus in vivo cannot be ruled out, but seems a remote possibility in view of the experiments in vitro.

One may speculate that the dermatologic effect of calciferol is to bring about an activation of devitalized tissue thus upsetting the static and prolonged balance between the resistance of the host and the weakly invasive powers of the bacillus. With increased oxygen consumption of the individual tissue cells, a proliferation occurs which literally suffocates the enclosed tuberculous structure. The immediate reaction is an inflammatory one which eventuates in the formation of scar tissue.

Distribution of Vitamin D in the Body Investigators using calciferol in treatment of other forms of tuberculosis are aware of the distribution of the drug in the body. In 1939, Vollmer¹⁴ administered massive doses of vitamin D to a dying infant three days before death. Postmortem bioassays of the various organs revealed that the major portion of the vitamin D was stored in the skin, brain and liver. No

12 Gelfan, S. The Effect of Viosterol upon Oxygen Consumption of Frog's Muscle. *Am J Physiol* 113:464, 1935.

13 Feeny, P. J.; Sandiland, E. L., and Franklin, L. M. Calciferol in Tuberculosis. Review of One Hundred and Fifty Cases of Lupus Vulgaris, Review of Twenty-One Cases of Pulmonary Tuberculosis, *Lancet* 1:438, 1947.

14 Vollmer, H. Distribution of Vitamin D in the Body After Administration of Massive Doses, *Am J Dis Child* 57:343 (Feb) 1939.

appreciable amounts were found in the lungs, spleen or bones Windorfer¹⁵ reported a similar experiment in 1938, with similar results. Thus no improvement could be expected in pulmonary tuberculosis unless, perhaps, the calciferol were utilized in a form suitable for inhalation.

COMMENT

The treatment of cutaneous tuberculosis, and in particular of lupus vulgaris, has been greatly advanced by the use of calciferol, and the drug may be safely recommended. One need not have any particular experience with its use in order to give the method a trial. A careful evaluation of the patient's condition, however, is essential. Knowledge of the state of the lungs, an estimate of renal function and a careful evaluation of the general physical condition are all that is necessary in order to proceed with relative safety. Patients receiving calciferol should be seen often at least once a week, and should be instructed to stop taking the vitamin at once if nausea, anorexia, giddiness or other unusual symptoms develop. Patients with large areas of involvement or with tuberculous adenitis, or those unable to tolerate the usual dosage, should only be treated in the hospital.

The one tuberculous cutaneous condition which warrants prolonged trial and adjustment of dosage to enforce tolerance is lupus vulgaris. The results in the other forms of cutaneous tuberculosis have not been striking enough to justify any risk being taken in order to continue the treatment in the presence of mild signs of intolerance or to justify continuation of the treatment for periods longer than three months when no improvement is noted.

The treatment of lupus vulgaris is of great economic and social importance. Calciferol therapy is a definite advance over the best that could have been expected of the Finsen treatment. It has shortened the period of treatment, has saved the patient much loss of time and has made him independent, to some degree, of strict supervision and tedious routine. The treatment can usually be carried out without the patient's changing his residence or becoming an inmate of an institute.

If the calciferol treatment of lupus vulgaris is a great help in areas where the disease is endemic, it is an even greater help to dermatologists in this country. Here we have no Finsen institutes, formerly, when lupus vulgaris was encountered, treatment was haphazard at best, because the highly technical facilities and knowledge necessary to carry out even a modified Finsen treatment were lacking. With the advent of calciferol therapy, a reasonably successful and safe treatment for lupus vulgaris is available. The method of its use, the dangers and

15 Windorfer, A. Ueber die Vitamin-D-Resorption bei Verabreichung hoher Dosen C Vitamin D-Stoss, *Klin. Wchnschr.* **17** 228, 1938.

the therapeutic possibilities can easily be learned. Since the method is not a specific and may not actually cure lupus vulgaris, further search for therapeutic combinations and improvements in its use is urged.

SUMMARY AND CONCLUSIONS

A series of 25 cases of cutaneous tuberculosis treated with massive doses of calciferol (vitamin D₂) is reported.

From the results and experience obtained, the following conclusions are drawn:

1. Calciferol is a valuable adjunct in the treatment of cutaneous and nodular tuberculosis.
2. It has exceptional value in the treatment of lupus vulgaris.
3. Toxic reactions may be encountered.
4. The precise mode of action in lupus vulgaris is not known.
5. Calciferol therapy combined with injections of streptomycin is worthy of further trial.

ABSTRACT OF DISCUSSION

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: Dr. Michelson has given an excellent evaluation of vitamin D therapy in cutaneous tuberculosis. I can substantiate, in their entirety, his observations.

Physicians in this country have now confirmed the effectiveness of calciferol in the treatment of lupus vulgaris, yet neither Chapoy, Dowling and Thomas nor any of us know how or why calciferol works. Calciferol, which is produced by the irradiation of the ergosterol of yeast, is strongly antirachitic and relatively nontoxic in therapeutic doses. It was originally thought to be the provitamin D in the skin which was activated by irradiation. Waddell (*The Provitamin D of Cholesterol*, *J Biol Chem* **105** 711, 1934) showed that irradiation of cholesterol produced a compound equal to cod liver oil in antirachitic potency, and, therefore, thirty times greater in that respect than irradiated ergosterol. The discrepancy in the antirachitic potency of irradiated ergosterol and cod liver oil was known before vitamin D₂, or 7-dehydrocholesterol, was known. The antirachitic activity of irradiated milk, cod liver oil and irradiated skin is due to this substance. What effect might it have in lupus vulgaris?

When ergosterol is irradiated, lumisterol, tachysterol, and then calciferol and suprasterol are produced. Tachysterol has little, if any, antirachitic property, but it does have a greater effect than calciferol in producing the excretion of phosphorus. Would it or the other closely related compounds be effective in lupus vulgaris?

Why do not those who have services where cutaneous tuberculosis is seen try the several other substances that make up the vitamin D family to determine their therapeutic effectiveness? Each member of the group has a somewhat different effect on metabolism, perhaps using them all might help us to learn how vitamin D acts in cutaneous tuberculosis.

It should again be emphasized that calciferol is a toxic drug. It produces hypercalcemia, hyperphosphatemia and a rise in the nonprotein nitrogen level of the blood. In large doses, it withdraws calcium and phosphorus from bones and increases their excretion in the urine. If given in large doses for long periods of time, osteitis fibrosa cystica, soft tissue calcification or even death, often from renal calcification and failure, may ensue.

Dr Michelson has discussed the toxic symptoms. It behooves us all to follow our patients closely and make sure that the drug is withdrawn when toxic symptoms occur and that calciferol is not taken, even in moderately large doses, independently for long periods of time by our patients.

Dr MARION SULZBERGER, New York. Since beginning our studies of calciferol at the New York Skin and Cancer Unit, I have been amazed at the number of cases of lupus vulgaris we were able to find among the foreign born in New York. In studies carried out in our institute, Dr Frances Pasher and her collaborators published data indicating that vehicles used for calciferol are apparently not so important as the European authors first seemed to think. Alcoholic and oily vehicles seemed to have roughly equivalent effects. I cannot agree entirely with Dr Michelson regarding the explanation that the peculiar geographic distribution of lupus vulgaris is due simply to differences in nutrition and sunlight. Switzerland, in general, has a high nutritional standard with plenty of eggs, butter and milk and with the hours of sunlight very high in many areas, yet lupus vulgaris is common there. In many parts of the United States, even in the slums and mining districts with few hours of sunlight and with poor nutrition, lupus vulgaris is almost entirely absent. In South America, there is very little, if any, lupus vulgaris, even when nutrition is poor and exposure to sunlight low. I think the explanation is much more complex than the one given by Dr Michelson, although there is no denying that both sunlight and diet do play a role in the incidence of tuberculosis. I was deeply interested in hearing Dr Michelson's excellent report, and particularly his complete confirmation of the Jadassohn-Lewandowsky law. Whenever and wherever pathogenic micro-organisms are being damaged or slowly destroyed by immune processes in the tissues, sarcoid structures tend to appear. I should like to confirm Dr Michelson's statement that on rare occasions the lesions of lupus vulgaris may be observed to turn into sarcoid lesions and vice versa. Such cases were reported long before the use of calciferol. Moreover, concomitant with these transformations, the response of the skin to the tuberculin test changes from hyperergic to hypoergic, or vice versa. Has Dr Michelson been able to carry out quantitative tuberculin tests of the skin in his cases of lupus vulgaris in which a transformation to sarcoid lesions was noted under therapy with calciferol to see whether then, also, the tuberculin sensitivity has shifted from hyperergy to hypoergy?

Dr PAUL O'LEARY, Minneapolis. Our experience in the use of streptomycin in the treatment of cutaneous tuberculosis and tuberculids has not been sufficiently encouraging to continue to use the antibiotic drug alone, similarly, my limited experience with calciferol in the treatment of lupus vulgaris has been far from encouraging. However, the combination of calciferol and streptomycin seems to offer results superior to those obtained from the use of either of these agents alone. Studies of blood calcium and phosphorus levels are not always so revealing as is the patient's reaction to calciferol. Evidence of vitamin D intoxication may be manifested by loss of appetite, lassitude, gastrointestinal upsets, headache or nausea before evidence of hypercalcemia appears in the form of increased blood levels.

It seems to me that lupus vulgaris should now be subjected to the newer cultural and inoculation experiments for tubercle bacilli. I recently reviewed some forty-four articles dealing with bacteriologic studies in lupus vulgaris, none of them included a report of the modern cultural and inoculation experiments that may now be carried out on animals.

Feldman, who has done outstanding work in experimental tuberculosis, believes that much is to be done to prove that the bacillus recognized in lupus vulgaris is the same organism which causes pulmonary tuberculosis. I believe that with

present knowledge one is limited to saying that lupus vulgaris is a disease seen in patients who have tuberculosis. The lack of improvement in lupus vulgaris and the apparent cure of pulmonary and other forms of tuberculosis after administration of streptomycin and, conversely, the improvement in lupus vulgaris and lack of benefit in pulmonary tuberculosis after administration of calciferol, raise questions that now need answering.

DR PAUL E BECHET, New York. About a week before I left the East, I saw, at the Montreal General Hospital during a meeting of the Atlantic Dermatological Conference, a group of 6 or 7 patients with chronic lupus vulgaris with extensive involvement. All sorts of treatment had been tried, with little success. Dr Fred Burgess, who presented the patients, had been using calciferol in treatment, with spectacular results. One patient showed complete recession of the disease. All the others were greatly improved. The new treatment shows great promise and in my opinion is a step forward in the therapy of lupus vulgaris, however, it will take several years properly to determine its value.

DR HARRY ARNOLD, Honolulu, T H. Dr Sulzberger's remarks prompt me to mention an article (Lima, L de S, and Souza Campos, N. Immuno-Biologic Anomalies in Leprosy, *Internat J Leprosy* 16 9, 1948) in which inversion of the reaction to the Mitsuda-Rost test, both from positive to negative and from negative to positive, is described. Corresponding changes are usually observed in the clinical form of the disease.

DR HENRY E MICHELSON, Minneapolis. I believe that the most important thing to emphasize in Dr Curtis's discussion is that results in treatment of lupus vulgaris come when one is using almost toxic doses of calciferol. Small doses are of no value. We have found it advisable in a few cases to reduce the dose to 10,000 units three times daily and have found this worth while. When one is considering lupus vulgaris, one must think of the soil and the type of infection. I definitely believe the condition to be due to tuberculosis, but it is an odd form of tuberculosis and it is dependent on a great many factors in the patient's nutritional make-up. In answer to Dr Sulzberger, the cases in Switzerland are largely in patients from the peasant class. The disease is noted more often in certain valleys, where the hygiene is notably poor, than in others.

I have often stated that the pathologic factors of lupus vulgaris and those of sarcoid could not be distinguished from each other in certain cases, I am sure that this is true. I was surprised to find, after treatment with calciferol, that the histologic picture often became sarcoidal. I have not performed any tests to show that the tuberculin reaction changes with the histologic features, but I believe Macrae did. He stated that the tuberculin reactions increase in intensity and run parallel with elevation of the sedimentation rate. The phenomenon takes place during the first three weeks of treatment and then settles down.

Dr O'Leary will have to read a tremendous amount of literature if he wishes to find all the reports on bacilli in lupus vulgaris. There are many, many of them. It must be remembered that lupus vulgaris was treated by surgeons long before it was by dermatologists. The disease was not considered tuberculous until after Koch's work. The reasons for considering it tuberculous now are many. The finding of the bacilli, the tuberculin reaction, the history and the frequent presence of other forms of tuberculosis are just a few of them.

SOME DERMATOLOGIC EPONYMS

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EPONYMIC designation, like any abbreviation, is intended to be a short cut to description, but to serve this purpose even occasionally used terms should be widely understood. It is the purpose of this list to bring together for convenient reference most of the eponymic entities of interest to the dermatologist. Some entities which are not easily found in standard texts on dermatology, or which are rarely encountered, are listed with definitions and references. Other entities, either partially eponymic, of great familiarity, or whose synonyms are self explanatory, are simply listed for the sake of completeness. No biographic or historic data are included, as these aspects of the subject have been thoroughly covered by Goodman.¹

ACHARD-THIERS SYNDROME Obesity and hypertrichosis of the face of masculine distribution in women without other signs of virilism²

ADDISON'S DISEASE

ALBRIGHT'S SYNDROME An endocrine disturbance consisting of polyostotic fibrous dysplasia, with cutaneous pigmentation in both sexes and precocious puberty in girls³

ALMEIDA'S DISEASE Paracoccidioidal granuloma, Brazilian blastomycosis

ANDREWS' PUSTULAR DERMATITIS

BAELZ'S DISEASE Superficial suppurative cheilitis glandularis

BALZER'S ADENOMA SEBACEUM

From the Department of Dermatology, University of Illinois College of Medicine, Service of Dr Francis E Senear (Dr Haeberlin), and the Department of Dermatology, Northwestern University Medical School, Service of Dr Edward A Oliver (Dr Garrard)

1 Goodman, H. Eponyms of Dermatology, Arch Dermat & Syph **9** 675 (June) 1924

2 Shallow, T. A. Adrenal Tumour Producing the Achard-Thiers Syndrome, Ann Surg **98** 297 (Aug) 1933

3 Albright, F., Butler, A. M., Hampton, A. O., and Smith, P. Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females, New England J Med **216** 727 (April 29) 1937

- BAZIN'S BUCCAL PSORIASIS Leukoplakia buccalis
- BAZIN'S DISEASE Tuberculosis indurativa, erythema induratum
- BEHCET'S SYNDROME Triple symptom complex
- BEIGEL'S DISEASE Trichorrhæxis nodosa, chignon fungus
- BESNIER'S LUPUS PERNIO Acrodermatitis pustulosa hiemalis (Crocker), necrotizing chilblains (Allen)
- BESNIER'S PRURIGO Atopic dermatitis, neurodermatitis disseminata, atopic eczema, flexural eczema
- BLOCH-SULZBERGER DISEASE Incontinentia pigmenti
- BOCKHART'S IMPETIGO Superficial staphylococcic folliculitis
- BORST-JADASSOHN INTRAEPIDERMAL EPITHELIOMA
- BOWEN'S DISEASE Precancerous dermatosis
- BRILL'S DISEASE Sporadic endemic typhus with erythematous macular and petechial exanthems
- BROOKE'S DISEASE Keratosis follicularis contagiosa
- BRUSHFIELD-WYATT SYNDROME Weber-Sturge syndrome
- BURGER'S DISEASE Thromboangitis obliterans
- BURGER-GRUTZ SYNDROME Xanthoma disseminatum and hepatosplenomegaly with cutaneous and mucosal lipidosis ⁴
- CARRION'S DISEASE Verruga peruana, Oroya fever
- CAZENAVE'S DISEASE Lupus erythematosus
- CIVATTE'S POIKILODERMA Reticulated pigmented poikiloderma
- CLUTTON'S JOINTS Syphilitic hydrarthrosis
- CSILLAG'S DISEASE Dermatitis lichenoides chronica atrophicans, lichen sclerosis et atrophicus, lichen albus of Zumbush
- CUSHING'S DISEASE Pituitary basophilism
- DARIER'S DISEASE Keratosis follicularis, keratosis vegetans
- DARIER-FERRAND DISEASE Dermatofibrosarcoma protuberans, progressive and recurrent dermatofibrosarcoma
- DARIER-ROUSSY SARCOID Subcutaneous sarcoid
- DARLING'S DISEASE Histoplasmosis
- DERCUM'S DISEASE Adiposis dolorosa
- DEVERGIE'S DISEASE Pityriasis rubra pilaris
- DUHRING'S DISEASE Dermatitis herpetiformis
- DUKE'S DISEASE (EXANTHEMA SUBITUM) Fourth disease
- EHLERS-DANLOS SYNDROME Hyperelasticity of the joints and skin, subcutaneous tumors and fragility of the skin with faulty healing leading to scar formation ⁵
- ENGMAN'S INFECTIOUS ECZEMATOID DERMATITIS Dermatitis infectiosa eczematoides
- ERB'S SYNDROME Syphilitic spastic spinal paralysis (paraplegia due to syphilitic transverse myelitis) ⁶

⁴ Ormsby, O S, and Montgomery, H Diseases of the Skin, ed 6, Philadelphia, Lea & Febiger, 1943, p 649

⁵ Ronchese, F Dermatorrhæxis with Dermatochalasis and Arthrochalasis (So-Called Ehlers-Danlos Syndrome), Am J Dis Child **51**:1403 (June) 1936

⁶ Peters, E E The Spinal Fluid in Erb's Syphilitic Spinal Spastic Paraplegia, Am J Syph, Gonorr & Ven Dis (Jan) 1941

- FELTY'S SYNDROME Chronic deforming arthritis with splenomegaly, lymphadenopathy, leukopenia, cutaneous pigmentation and dusky nodules⁷
- FORDYCE'S DISEASE Pseudocolloid of the lips
- FOX-FORDYCE DISEASE Chronic itching papular eruption of the axilla and pubes
- FRANCIS' DISEASE Tularemia
- FREY'S SYNDROME Auriculotemporal nerve syndrome Increased secretion of the parotid gland with homolateral hyperhidrosis in the distribution of the auriculotemporal nerve⁸
- GAUCHIER'S DISEASE Large cell splenomegaly, cerebroside histiocytosis
- GILCHRIST'S DISEASE Brazilian blastomycosis
- GRONBLAD-STRANDBERG SYNDROME Angioid streaks of the retina, associated with pseudoxanthoma elasticum⁹
- GOUGEROT AND BIUM DISEASE Pigmented purpuric lichenoid dermatitis
- GUIE'S DISEASE Atrophy of thyroid gland with myxedema
- HABERMANN'S DISEASE Pityriasis lichenoides et varioliformis acuta
- HALLER AND HALLER DISEASE Chronic benign familial pemphigus, recurrent herpetiform dermatitis repens, bullous Darier's disease, dyskeratosis bullosa hereditaria
- HALLOPEAU'S ACRODERMATITIS Acrodermatitis continua, dermatitis repens
- HALLOPEAU-LEREDDE ADENOMA SIBACUM
- HAND-SCHULLER-CHRISTIAN DISEASE Christian-Schuller disease, systemic reticuloendothelial granuloma
- HANSEN'S DISEASE Leprosy, Leontiasis, spedalskhed, *Aussatz*
- HANTHAUSEN'S DISEASE Keratoderma climactericum
- HEBRA'S PITIRIASIS RUBRA
- HERNOCH'S PURPURA Purpura abdominalis
- HERRFORDT'S DISEASE Uveoparotitis, Uveoparotid fever
- HODGKIN'S DISEASE Malignant lymphogranulomatosis
- HOPF'S ACROKERATOSIS VERRUCIFORMIS A hereditary condition characterized by verrucous lesions resembling those of epidermodysplasia verruciformis, occurring on the dorsa of the hands and feet with some involvement of the palms and flexor surfaces of the fingers, wrists and forearms but never occurring on the face Histologically, the disease may be differentiated from epidermodysplasia verruciformis by the absence of basket-weave appearance of the stratum corneum¹⁰
- HUNT'S SYNDROME Herpes zoster involving the geniculate ganglion, characterized by auricular and facial palsy, pain, vertigo and tinnitus with vesicles on the external ear¹¹

7 Felty, A. R. Chronic Arthritis in the Adult, Associated with Splenomegaly and Leucopenia. A Report of Five Cases of an Unusual Clinical Syndrome, *Bull Johns Hopkins Hosp* **35** 16 (Jan) 1924

8 Frey, L. Le syndrome du nerf auriculo-temporal, *Rev neurol* **2** 97 (Aug) 1923

9 Gronblad, E. Angioid Streaks—Pseudoxanthoma Elasticum, *Acta ophth* **7** 329, 1929

10 Loveman, A. B., and Graham, P. V. Acrokeratosis Verruciformis (Hopf), *Arch Dermat & Syph* **43** 971 (June) 1941

11 Hill, F. T. Herpes Zoster Oticus. Report of Three Cases, *Ann Otol, Rhin & Laryng* **45** 666 (Sept) 1936

- HUTCHINSON'S LUPUS PERNIO Lupus erythematosus resembling chilblains
- HUTCHINSON'S MELANOTIC WHITLOW Malignant melanoma arising under the nail
- HUTCHINSON'S SYNDROME Hutchinson's triad (a combination of the following stigmas of congenital syphilis interstitial keratitis, peg-shaped, notched incisors and nerve deafness ¹²)
- HYDE'S PRURIGO NODULARIS Lichen obtusus corneus
- JACOB'S POIKILODERMA VASCULARE ATROPHICANS
- JACOB'S ULCER Rodent ulcer
- JACQUET'S ERYTHEMA Napkin dermatitis
- JADASSOHN'S BLUE NEVUS
- JULIUSBERG'S DISEASE Pityriasis lichenoides chronica, parapsoriasis en gouttes of Brocq (guttate parapsoriasis)
- KAST'S SYNDROME The association of hemangiomas with chondromas or dyschondroplasia ¹³
- KAPOSI'S MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA
- KAPOSI'S VARICELLIFORM ERUPTION Herpes simplex superimposed on chronic eczema ¹⁴
- KREIBICH'S EXUDATIVE NEURODERMATITIS
- KYRLE'S DISEASE Hyperkeratosis follicularis et para-follicularis in cutem penetrans
- LEINER'S DISEASE Erythroderma desquamativa, universal dermatitis of children at the breast
- LETTERER-SIWE DISEASE Lipidosis or granuloma of the reticuloendothelial system, with petechial exanthem and purpura but without cutaneous xanthoma ¹⁵
- LEWANDOWSKY-LUTZ DISEASE Epidermodysplasia verruciformis
- LEWANDOWSKY'S ROSACEA-LIKE TUBERCULID
- LIBMAN-SACKS SYNDROME A variety of acute lupus erythematosus disseminatus
- LIPSCHUTZ' DISEASE Ulcus vulvae acutum
- LUBARSCH-PICK SYNDROME Atypical amyloidosis with macroglossia ¹⁶
- MAFFUCCI'S SYNDROME Dyschondroplasia associated with hemangiomas ¹⁷
- MAJOCCHI'S DISEASE Purpura annularis telangiectodes
- MAJOCCHI'S GRANULOMA A kerion type, superficial fungous infection
- MEIGE'S DISEASE Milroy's disease

12 Cole, H N Congenital and Prenatal Syphilis, J A M A **109** 580 (Aug 21) 1937

13 Carleton, A, and Robb-Smith, A H T Kast's Syndrome (Multiple Hemangiomata Associated with Chondromata or Ollier's Dyschondroplasia), Brit J Dermat **51** 91 (Feb) 1939

14 Lynch, F W, and Steves, R J Kaposi's Varicelliform Eruption, Arch Dermat & Syph **55** 327 (March) 1947

15 Wallgren, A Systemic Reticuloendothelial Granuloma, Non-Lipoid Reticuloendotheliosis and Schuller-Christian Disease, Am J Dis Child **60** 471 (Sept) 1940

16 Bernard, W G, Smith, F B, and Woodhouse, J L Atypical Amyloidosis with Macroglossia, J Path & Bact **47** 311 (Sept) 1938

17 Carleton, A, Elkington, J St C, Greenfield, J G, and Robb-Smith, A H T Maffucci's Syndrome (Dyschondroplasia with Haemangeiomata), Quart J Med **11** 203 (Oct) 1942

MELFNY'S ULCLR An acute, undermining and burrowing streptococcic infection of the skin and the subcutaneous tissues ¹⁸

MIBELLI'S ANGIOKLATOMA

MIBILI'S DISFASI Porokeratosis

MILIAN'S ERYTHILMA Ninth day erythema

MIIROY'S DISI ASF Tropholymphe'dema, chronic hereditary trophedema, hereditary edema of the legs, Meige's disease, familial hereditary edema

MOELLER'S GLOSSITIS Chronic superficial excoriations of the tongue, chronic glossitis

MORVAN'S DISFASF Syringomyelia

NTUMANN'S DISEASF Pemphigus vegetans

NICOLAS-FAURE-DURAND DISLASF Lymphogranuloma venereum

NIFMANN-PICK DISEASE Lipid histiocytosis

OSLER-RENDU-WIEBER SYNDROME Hereditary hemorrhagic telangiectasia

PAGET'S DISFASF Eczema epitheliomatousum

PARKS-WIEBER SYNDROME Hemangiectatic hypertrophy of the limb (hypertrophy of an entire extremity due to congenital ectasia of the blood vessels) Superficial hemangiomatous elements with verrucous lesions, pigmentations and ulceration may be present ¹⁹

PAUTRIER-WORINGER SYNDROME Lipomelanotic reticulosis

PLUMMER-VINSON SYNDROME Dysphagia due to chronic glossitis, cheilitis and pharyngitis, with hypochromic anemia and koilonychia ²⁰

PRINGLE'S ADFNOMA SIBACEUM

QUEYRAT'S ERYTHROPIASIA

QUINCKE'S DISEASE Angioneurotic edema

QUINQUAD'S DISEASF Folliculitis decalvans

RAYNAUD'S DISEASE Symmetric gangrene of the extremities

REITER'S SYNDROME Arthritis, urethritis and conjunctivitis, not due to the gonococcus, sometimes associated with keratosis blennorrhagia ²¹

ROMBERG'S DISFASF Progressive hemiatrophy of the face An atrophic process involving the skin, subcutaneous tissues and bone, in the distribution of the fifth cranial nerve The disease usually occurs in the second decade of life ²²

ROTHMUND'S SYNDROME ²³

SAVILL'S DISEASE Epidemic exfoliative dermatitis, a form of exfoliative dermatitis which occurred in epidemics among the older inhabitants of asylums and infirmaries in London England ²⁴

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- SCHAMBERG'S DISEASE Progressive pigmentary dermatosis
- SCHAUMANN'S DISEASE Lymphogranulomatosis benigna, a generalized form of sarcoidosis with lesions characteristically on the skin, in the bones and in various organs, including the lungs, liver, spleen and uveal tract ²⁵
- SCHONLEIN'S PURPURA. Purpura rheumatica, idiopathic nonthrombopenic purpura
- SCHWENINGER-BUZZI DISEASE Multiple benign tumor-like lesions of the skin
- SENEAR-USHER SYNDROME Pemphigus erythematodes
- SJÖGREN'S SYNDROME An association of keratoconjunctivitis sicca, xerostomia, rhinitis sicca and laryngitis sicca, in which the skin may show dryness, blueness as in Raynaud's disease, telangiectasis of the lips and finger tips, scleroderma-like changes and alopecia ²⁶
- SPIEGLER-FENDT SARCOID This entity is considered a lymphoblastoma It occurs in a localized form, resembling Boeck's sarcoid, and in a disseminated form, with lesions clinically resembling the Darier-Roussy type ²⁷
- ST ANTHONY'S FIRE Erysipelas
- STEVENS-JOHNSON SYNDROME A severe form of erythema multiforme, characterized by erosive lesions of the orificial mucous membranes, including those of the mouth, conjunctiva and genitalia, with fever, prostration and sometimes multiform lesions on the glabrous skin ²⁸
- STRYKER-HALBEISON SYNDROME Erythroderma with macrocytic anemia
- STILL-CHAUFFARD DISEASE Arthritis of the cervical portion of the spine, with anemia leukopenia, splenomegaly, enlargement of the lymph nodes and cutaneous pigmentations, especially on the cheeks ²⁹
- SUTZBERGER AND GARBE DISEASE Exudative, discoid and lichenoid chronic dermatitis
- SUTTON'S DISEASE Peradenitis mucosa necrotica recurrens, chronic aphthous stomatitis
- SWIFT'S DISEASE Acrodynia, erythredema polyneuropathy
- SYMMER'S DISEASE Brill-Symer disease, giant follicular lymphoblastoma
- THIBIERGE-WEISSENBACH SYNDROME The occurrence of calcinosis cutis circumscripta with scleroderma ³⁰
- UNNA-SANTI-POLLITZER DISEASE Parakeratosis variegata
- VIDAL'S DISEASE Lichen chronicus simplex, neurodermatitis
- VINCENT'S INFECTION Trench mouth
- 25 Michelson, H E Uveoparotitis A Sarcoid Reaction, Arch Dermat & Syph **30** 329 (Feb) 1939
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VOGT-KOYANAGI SYNDROME Bilateral uveitis, premature alopecia and graying of the hair and symmetric vitiligo, especially of the extremities, with dysacusia ³¹

VOLKMANN'S DISIASI Apostematous cheilitis glandularis

RECKLINGHAUSEN'S DISIASI Neurofibromatosis

WATERHOUSE-FRIDERICHSEN SYNDROME Fulminating meningococcic septicemia, vascular collapse and widespread purpuric lesions of the skin ³²

WEBER-CHRISTIAN SYNDROME Relapsing febrile nodular nonsuppurative panniculitis

WEBER-COCKayne SYNDROME A form of epidermolysis bullosa, localized to the hands and feet ³³

WEBER-STURGE SYNDROME Brushfield-Wyatt Syndrome Nevus flammeus, contralateral hemiparesis, epilepsy and calciferous shadows in the cerebral cortex on roentgenologic examination ³⁴

WERNER'S SYNDROME Scleroderma, poikiloderma, bilateral juvenile cataracts, pluriglandular dysfunction and precocious graying of the hair ³⁵

WELSHOF'S PURPURA Thrombopenic purpura

WILSON-BROCK DERMATITIS ENFOIATIVA

55 East Washington Street (3)

541 Lincoln Road

31 Carrasquillo, H F Uveitis with Poliosis, Vitiligo, Alopecia and Dysacusia (Vogt-Koyanagi Syndrome), Arch Ophth **28** 385 (Sept) 1942

32 Wright, D O, and Reppert, L B Fulminating Meningococcemia with Vascular Collapse (Waterhouse-Friderichsen Syndrome) Report of Four Adult Patients Who Recovered, Arch Int Med **77** 143 (Feb) 1946

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RECENT OBSERVATIONS ON GRANULOMA INGUINALE, WITH REPORT ON STREPTOMYCIN THERAPY

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IN RECENT years decided advances have been made in various aspects of the study of granuloma inguinale, such as in diagnosis,¹ cultivation of the etiologic agent,² experimental reproduction of the disease^{1a} and treatment.³ One hundred patients⁴ with laboratory-proved

Aided by a research grant from the United States Public Health Service
From the University of Georgia School of Medicine

1 (a) Greenblatt, R B , Dienst, R B , Pund, E R , and Torpin, R Experimental and Clinical Granuloma Inguinale, J A M A **111** 1109-1115 (Sept 16) 1939 (b) Anderson, K , Goodpasture, E W , and DeMonbreun, W A Immunologic Relationship of Donovan Granulomata to Granuloma Inguinale, J Exper Med **81** 41-50 (Jan) 1945 (c) Packer, H , Turner, H B , and Dulaney, A D Granuloma Inguinale of the Vagina and Cervix Uteri with Bone Metastases, J A M A **136** 327-329 (Jan 31) 1948 (d) Dienst, R B , Greenblatt, R B , and Chen, C H Laboratory Diagnosis of Granuloma Inguinale and Studies on the Cultivation of the Donovan Body, Am J Syph, Gonorr & Ven Dis , to be published (e) Chen, C H , Dienst, R B , and Greenblatt, R B Skin Reaction of Patients to Donovan Granulomata Antigen, to be published

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3 (a) Greenblatt, R B , Kupperman, H S , and Dienst, R B Streptomycin in the Therapy of Granuloma Inguinale, Proc Soc Exper Biol & Med **64** 389-390 (April) 1947 (b) Greenblatt, R B , Dienst, R B , Kupperman, H S , and Rein-stein, C R Granuloma Inguinale Streptomycin Therapy and Research, J Ven Dis Inform **28** 183-188 (Sept) 1947 (c) Kupperman, H S , Greenblatt, R B , and Dienst, R B Streptomycin in the Therapy of Granuloma Inguinale, J A M A **136** 84-89 (Jan 10) 1948

4 Since this article was submitted for publication 42 additional patients have been treated with streptomycin, and the patients comprising the total series of 142 cases have now been under observation for one to three years after treatment

(Footnote continued on next page)

cases of granuloma inguinale who have been treated at the University of Georgia during the past twenty months formed the basis of this study

The patients comprising this group were all Negroes. Their ages ranged from 18 to 70 years, and most of them were in the 20 to 40 year age groups. Sixty-five of them were men and 35, women (fig 1). Though most of them had been previously treated with antimonial substances, one third of them had not had any form of treatment

LESIONS

As a rule patients gave a history of having had a nodule which had developed on the genitalia or elsewhere. This nodule had gradually softened, with the accumulation of purulent material. Later, the skin

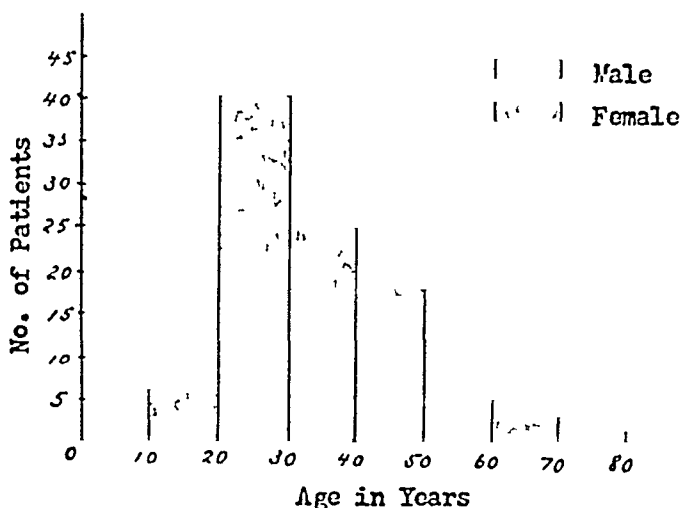


Fig 1—Distribution by sex in age groups

surface had excoriated and an ulcerative process set in. In more chronic cases papillated vegetations and elephantiasis were commonly seen. While most patients presented the classic picture of a friable, "beefy red," ulcerogranulomatous lesion, about 15 per cent of the patients had lesions resembling a wide variety of either venereal (e g, chancroid, lymphogranuloma venereum, syphilis) or nonvenereal (e g, cancer, condyloma acuminatum) diseases. As a matter of fact, in a series of 95 referred patients who had been given a diagnosis or even treated as having had granuloma inguinale for months, only 66 (70 per cent) actually had

In all, there has been a failure rate of about 10 per cent. Five of the patients for whom treatment failed proved recalcitrant to further streptomycin therapy. It is of interest to note that these 5 streptomycin-resistant patients were healed after the oral administration of aureomycin, the amounts varying from 25 to 70 Gm in doses of 500 mg every six hours.

the disease, the rest having the following disorders squamous cell carcinoma, 6, chancroid, 6, lymphogranuloma venereum, 11, condyloma acuminatum, 3, pyogenic granuloma, 2, and syphilis, 1

The most frequent sites of the lesions, in our series, were on the genital organs. These included the prepuce, the frenum, the glans penis, the shaft of the penis and the scrotum, in the male, the labium majus or minus, the clitoris, the fourchet, the vestibule, the vagina, the cervix and the uterus, in the female, and pubic and perineal regions, in both. Inguinal lesions ranked second. The adductor region of the thigh, which may be designated as the perigenital zone, and the perianal region were also commonly involved through direct extension and

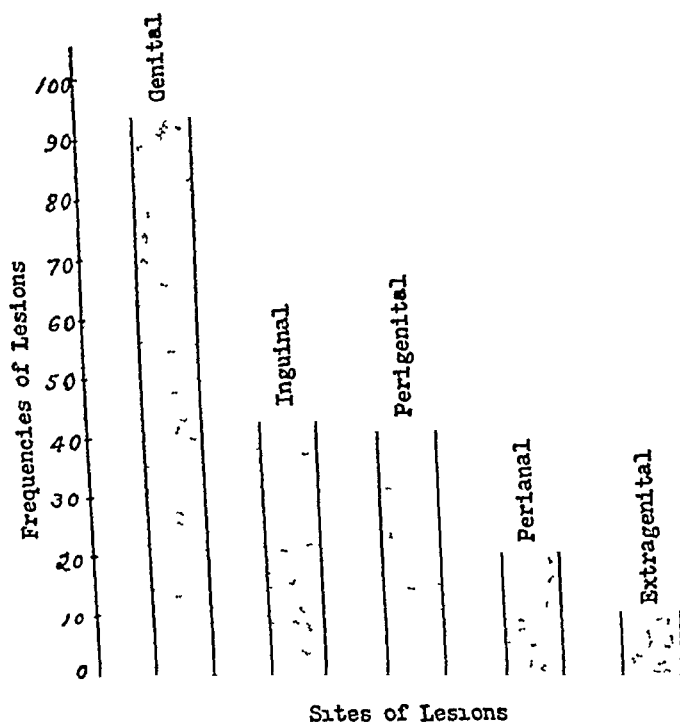


Fig 2—Distribution of sites of lesions

contact with other lesions. Nevertheless, there were 2 patients with perianal lesions alone. Extragenital lesions, either concurrent or independent, were least common. They occurred in 7 per cent with involvement of almost any part of the body, such as the tongue, lip, gum, palate, postauricular region, neck, trunk, abdomen, buttock, finger and leg. The size of the lesion also varied a great deal, ranging from 1 to 300 sq cm in the lesions measured. Except in very chronic cases, it seemed to be proportional to the duration of the disease (fig 2).

It was not infrequent to find other diseases associated with granuloma inguinale. Fusospirochetosis was by far the commonest. It occurred in 21 per cent of all cases. Other venereal diseases, such as chancroid, lymphogranuloma venereum, syphilis and gonorrhea, were

found to coexist. In 1 patient all major and minor venereal diseases were present, with the possible exception of chancroid. In addition, fusospirochetosis was superimposed on his granulomatous lesions.

METHOD OF ESTABLISHING DIAGNOSIS

Direct tissue smear examination was routinely employed in our studies. Before the smear was taken, the most typical area, i. e., the most reddish-looking and friable area, was chosen and cleaned well with a cotton applicator. A small piece of the granulomatous tissue, about 2 cu mm and not larger, was nipped off with the corners of two slides and firmly pressed with a grinding motion between the slides until a thin smear was obtained. Then the slides were pulled apart by sliding sidewise one from the other. In this way two smears were made. After they had been allowed to dry they were stained with a modification of Wright's stain^{4a} for one and one-half minutes, then an equal quantity of distilled water was added and staining continued for another three or four minutes. When unruptured inguinal pseudobuboes were found, smears were made from the aspirated pus.

With an oil immersion lens a search was made for the typical Donovan bodies in the cytoplasm of monocytes. If this procedure had been followed without finding the Donovan body and the clinical picture was highly suggestive of granuloma inguinale, repeated smears were taken on successive days for three or four days. Meanwhile, the superficial secondary contaminants, such as fusiform bacilli and spirochetes or other bacteria, were eliminated as far as possible with the use of penicillin or sulfonamide drugs, as was indicated. On more than one occasion, Donovan bodies were found after such preliminary treatment.

In rare cases (three in our series) in which Donovan bodies could not be found in original tissue smears, a specimen was removed for biopsy, and tissue smears and sections from this material revealed typical intramonocytic organisms. Biopsy of tissue also served to determine the possibility of other diseases, such as cancer and syphilis. No patient was included in this series unless diagnosis was established by demonstration of Donovan bodies, either in tissue smears or in biopsy specimens.

TREATMENT

Since it was our purpose to determine the effectiveness of streptomycin, other medication which might effect the Donovan body, whether general or topical, was not used. Fusospirochetosis, if present, was first treated with one or two injections of 300,000 units of penicillin in oil and wax (U. S. P.) intramuscularly. Then streptomycin was given in six equally divided doses at four hour intervals by the intramuscular route. The first 32 patients received a daily dose of 0.3 to 2.0 Gm for from six to sixty-two days, with an average of twenty-two days. Since the period of treatment was too prolonged and since there had been frequent recurrences, the dosage was later increased to 4 Gm a day for five days, with a total dose of 20 Gm. For patients with very extensive lesions the dose was advisedly increased up to 40 Gm, but not more (table 1). In all instances the amount of streptomycin to be given at each injection was dissolved in 2 cc of distilled water containing a small amount of procaine hydrochloride, the latter being used to alleviate local irritation and pain.

4a Formula: methanol (free from acetone), 485 cc, glycerin, 15 cc, and Wright's stain (powder form), 1 Gm.

Streptomycin suppositories given at three hour intervals were tried on 4 patients. The first 2 patients, with both genital and inguinal lesions, were given rectal suppositories with a daily dose of 4 Gm for nine days, plus 8 Gm for seven days for one and 4 Gm for ten days for the other. The next 2 patients, 1 with a lesion at the introitus vaginae and the other with a lesion on the lower abdomen wall, were each given 4 Gm daily for five days per vagina. Dibucaine hydrochloride (nupercaine hydrochloride®) ointment was used in the patient with the vaginal lesion ten minutes before each insertion of the vaginal suppository, to prevent burning pain due to the suppository.

TOXIC MANIFESTATIONS

Of all patients treated with streptomycin pruritus developed in 3 and burning sensations in the eye in 1. These conditions were readily controlled by the administration of diphenhydramine hydrochloride (benadryl hydrochloride®) or temporary suspension of streptomycin. However, a fifth patient had, in addition to pruritus, a generalized

TABLE 1—*Dosage and Results*

Total Number of Patients Treated, 100 (Male, 65, Female, 35)					
Dosage *			Results		
2 Gm or Less per Day for Average of 22 Days	4 Gm per Day for 5 Days	4 Gm per Day for 6-10 Days	Successful	Recurrence	Failure
32			24 (75%)	6 (19%)	2 (6%)
	61		57 (93%)	4 (7%)	0 (0%)
		7	7 (100%)	0 (0%)	0 (0%)

* All doses were given intramuscularly

urticarial and a circumoral vesicular eruption. He did not respond to the antihistaminic drug, and treatment with streptomycin had to be discontinued. Five months later he came back with a recurrent lesion and was retreated with the 4 Gm per day schedule. This time only generalized urticaria appeared, and with diphenhydramine hydrochloride he was able to take a seven and one-half day (30 Gm) treatment without further difficulty.

Transient mild pyrexia, unnoticed by patients themselves, starting on the second and subsiding on the third or fourth day, was observed in almost everyone treated with the 4 Gm per day schedule. Involvement of the eighth nerve, on the other hand, was not encountered in our series.

RESULTS

During the first period, when patients were receiving a daily dose of 2 Gm or less, the response was good but rather slow. Donovan bodies often persisted up to ten days, and lesions took many weeks to

heal Two patients failed to respond to 1 Gm per day for twenty-eight days and 2 Gm per day for thirty days, respectively (table 2) But with the 4 Gm per day dosage, signs of improvement were usually noticed as early as twenty-four hours after the beginning of treatment The feeling of soreness was distinctly alleviated, lesions became drier and cleaner, and healthy granulation tissue began to appear, smears taken at this time showed some degree of disintegration of Donovan bodies, with slight decrease in their number After forty-eight hours, amelioration of symptoms was usually obtained, and Donovan bodies showed further disintegration and decrease in number In favorable cases complete disappearance of Donovan bodies and beginning of epithelization were seen at the end of the third or fourth day and complete healing at the end of the fifth or sixth day However, in

TABLE 2—*Recurrences and Failures*

Number of Patients, 12 (Male, 10, Female, 2)		Results
Original Dosage	Dosage for Retreatment	
0.3 Gm /day for 11 days (3.3 Gm)	4.0 Gm /day for 10 days (40.0 Gm)	Healed
0.3 Gm /day for 12 days (3.6 Gm)	4.0 Gm /day for 7½ days (30.0 Gm)	Healed
0.3 Gm /day for 30 days (10.5 Gm)	4.0 Gm /day for 5 days (20.0 Gm)	Healed
4.0 Gm /day for 5 days (20.0 Gm)	4.0 Gm /day for 10 days (40.0 Gm)	Healed
0.6 Gm /day for 11 days (6.6 Gm)	4.0 Gm /day for 7½ days (30.0 Gm)	Healing
1.0 Gm /day for 13 days (13.0 Gm)	4.0 Gm /day for 10 days (40.0 Gm)	Healing
1.0 Gm /day for 5 days (20.0 Gm)	4.0 Gm /day for 10 days (40.0 Gm)	Healing
1.0 Gm /day for 25 days (25.0 Gm)	1.5 Gm /day for 41 days (61.5 Gm)	Failure
	4.0 Gm /day for 10 days (40.0 Gm)	
2.0 Gm /day for 10 days (20.0 Gm)	4.0 Gm /day for 10 days (40.0 Gm)	
1.0 Gm /day for 44 days (44.0 Gm)	To be re-treated	
4.0 Gm /day for 5 days (20.0 Gm)	To be re-treated	Failure
4.0 Gm /day for 5 days (20.0 Gm)	Patient died of recurrence (1) untreated	

most cases Donovan bodies disappeared at the end of a five day course of streptomycin and complete healing, with scar formation, occurred in one to two weeks In cases with more extensive lesions or in those in which the lesions remained moist or in apposition to other body surfaces, complete healing was sometimes delayed for from two to three months, in spite of the fact that Donovan bodies had disappeared within the usual time interval

In those patients treated with rectal suppositories no improvement was felt or observed at all The patient who received vaginal suppositories for her vaginal lesions, however, did have complete surface healing, with smears free from Donovan bodies after two weeks, an area of slight induration and discoloration being left The second patient receiving vaginal suppositories for her abdominal lesion also had some improvement, with surface healing, but the area was still indurated and elevated Smears taken at the end of treatment were

positive for Donovan bodies, however, at the end of six weeks healing was complete

FOLLOW-UP STUDIES

All patients, after dismissal, were asked to return regularly for rechecks at least every two months and in special cases as often as every week. To date, about 80 per cent of our patients have been followed in this manner for from six to twenty months, over half of them having been followed for more than one year. During this period 10 patients have returned with a recurrent lesion, 6 from the group treated with 2 Gm or less per day and 4 from the group treated with 4 Gm per day for five days. There have been no recurrences in those treated with 4 Gm per day for from six to ten days (table 1). It must be added that all recurrences up to now have occurred within four months after the completion of therapy.

Seven of the patients with recurrences have been re-treated with the 4 Gm per day schedule for from five to ten days, with complete healing in each case. Two patients have not been re-treated. One patient, who failed to return, died several months later with what may be accepted as having been a recurrence. His relative said that he was "eaten away with sores all over his front and back."

The 2 patients who represented primary failures were re-treated with 4 Gm per day for ten days, without success. They were then given antimonial substances. The first one received 3 cc of anthiomaline[®] (antimony and lithium thiomalate), equivalent to 30 mg of antimony, intramuscularly three times a week for one and one-half months, with the result that all lesions were healed before she was discharged from the hospital. Injections are being continued once a week for another six months to prevent a recurrence. The second received similar therapy for one month, but no response was obtained. Because stilbamidine[®] (4,4'-stilbenedicarboxamidine) proved so effective in treatment of leishmaniasis,⁵ the last-mentioned patient was given a trial course of this drug, consisting of fifteen doses of 150 mg each in 10 cc of isotonic solution of sodium chloride, injected intravenously every other day. This treatment proved ineffective. Since the patient had a decidedly exuberant form of lesion, local applications of 25 per cent of resin of podophyllum N F in compound benzoin tincture U S P were made three times a week for three weeks. The result was very good then, and all the excessive granulation tissue regressed. Injections of anthiomaline[®] were resumed, and roentgen therapy was given one week after treatment with resin of podophyllum was started. The dosage of roentgen radiation was 200 and 90 r on the first and

⁵ Adams, A. R. D., and Yroke, W. Studies in Chemotherapy XXXIII. A Case of Indian Kala-Azar Treated with 4,4'-Diamidine Stilbene, *Ann Trop Med* 33 323-326 (Dec) 1939.

second days, respectively, and again 95 r per day for two days one month later. Within three months his lesions were completely healed, with scar formation. It must be added that, on account of the severe burning pain which usually follows the application of resin of podophyllum, its use is not indicated on very extensive lesions and lesions on more sensitive parts of the genitalia.

Both patients treated with rectal suppositories were immediately given a regular course of streptomycin to which they responded readily. The patient treated with vaginal suppositories for her vaginal lesion had a recurrence one month later. A five day course of treatment cleared her lesion completely. All these 3 patients have been included in the group treated with 4 Gm per day for five days. The lesion of the second patient treated with vaginal suppositories remains healed, and she is still under observation.

COMMENT

Granuloma inguinale, according to our observations, may be most appropriately defined as a chronic infectious disease of doubtful transmission caused by the so-called Donovan bodies and characterized by a slowly growing granulomatous process, usually affecting the genital organs—the inguinal and perianal regions and occasionally other parts of the body. It occurs chiefly in warm climates and among Negroes. (In this series all were Negroes, however, we have encountered 3 white patients with granuloma inguinale.) However, cases have been reported from almost every part of the world, and no race is exempt.⁶

Contrary to the old general belief that granuloma inguinale primarily involved the inguinal region—hence the name—we found that genital lesions greatly outnumbered inguinal ones. In all our cases the number of lesions in the genital zone was 81, as compared with 36 in the inguinal region. (This is a fact that has been recognized by many investigators.⁷) Moreover, we have observed that in most cases with inguinal lesions there had been antecedent lesions on the genitalia. With regard to extragenital lesions, they may occur on any part of the body. Therefore, this disease is by no means limited to the inguinal region, nor is it most frequently found in that region.

6 Harris, R. Granuloma Venereum. General Discussion with Report of a Case of Laryngeal Involvement, *Laryngoscope* 40:707-737 (Oct.) 1930.

7 Harris,⁶ Fox, H. Granuloma Inguinale. Its Occurrence in the United States, *J. A. M. A.* 87:1785-1789 (Nov. 27) 1926. Lewis, S. J. Granuloma Inguinale with Special Reference to Its Occurrence in the White Race, *South. M. J.* 25:836-840 (Aug.) 1932. Cole, H. N. Venereal Diseases with Particular Reference to Granuloma Inguinale and Lymphogranuloma Inguinale, *Pennsylvania M. J.* 109:580-585 (July) 1937. D'Aunoy, R., and von Haam, E. Granuloma Inguinale. *Am. J. Trop. Med.* 17:747-763 (Sept.) 1937.

The spread of lesions was usually by continuity and contiguity. However, lymphatic spread was necessarily common also, as there were many cases in which genital lesions were followed by or accompanied with inguinal lesions. In patients with both extragenital and genital lesions, the possibility of spread by a hematogenous route has been considered. Several attempts to culture Donovan bodies from the blood and bone marrow of such patients have been made but were unsuccessful. Recently Packer, Turner and Dulaney^{1c} have demonstrated organisms having the morphologic features of Donovan bodies in the blood of a patient who had systemic infection, with metastases to bone.

Experimental inoculations by ordinary scratch method with granuloma tissue on several volunteers all met with failure. It was therefore decided to make repeated scratch inoculations on 1 patient. An area on the anterior aspect of his thigh was chosen and scratched to gentle bleeding every day. Immediately a piece of fresh granuloma tissue was rubbed onto that area each time and then kept in constant contact with the abraded skin by adhesive plaster. This procedure was continued for thirty-one consecutive days, and finally there was not the slightest sign of "take" observable grossly or microscopically. Hence it is very doubtful whether granuloma inguinale could develop on normal or simply abraded skin. Other factors must come into play also. Whether or not this is true with regard to mucous membranes is to be determined. Suggestions have been made that lesions of granuloma are usually superimposed on other lesions, like chancroid or lymphogranuloma venereum. Although we have not done any experiment along this line, we have been greatly impressed by the fact that a majority of our patients had positive reactions to either the Ducrey or the Frei test, or both, as we routinely tested them.

The diagnosis of granuloma inguinale by laboratory method is the simplest and most accurate of the venereal diseases. A positive diagnosis can usually be established within a few minutes. The entire procedure consists of making tissue smears from the lesion, staining these with Wright's stain and examining them under the oil immersion lens for the typical intramonocytic Donovan bodies. However, a proper technic is of paramount importance. A smear taken from a poorly selected area or a smear that is improperly prepared may often give rise to a false negative result. Experience has taught us that the procedures as briefly outlined previously are most convenient and satisfactory. Thorough cleaning of lesions before the taking of smears and the suppression of secondary contaminants by means of drugs are helpful in that the presence of necrotic debris and numerous bacteria hinders the finding of Donovan bodies. Too thick a tissue smear leads to a similar difficulty. The modification of the ordinary Wright staining method is

recommended for demonstration of the capsular material of the Donovan bodies. Donovan bodies with slightly overstained capsules are more readily seen by the examiner.

It must be stressed that in making an initial diagnosis one should depend only on observations of Donovan bodies in the cytoplasm of monocytes, because extracellular ones can be confused with other encapsulated organisms, especially the Friedlander bacillus. The presence of only extracellular Donovan bodies, however, is an indication for more prolonged searching or the making of more smears.

If one may judge from the data presented in preceding paragraphs that many cases of granuloma inguinale resembled those of other diseases, and vice versa, the importance of having a laboratory diagnosis in every case cannot be overemphasized. Laboratory diagnosis should be used as a final check in all clinically diagnosed or suspected cases of granuloma inguinale. It is only then that one can deal with this disease confidently and intelligently.

The treatment of granuloma inguinale has long been a problem taxing the ingenuity of the physician. Many unfortunate victims have succumbed to it eventually or have died of intercurrent diseases. The socioeconomic consequences of this problem were presented by one of us.⁸ But since the demonstration of the specificity of antimonial compounds against this disease in 1912,⁹ the situation has become more favorable. Success in treatment was reported from different parts of the world. However, in our institution, as everywhere, more and more recurrences were seen as time went on, even in patients who had been treated for a long period. Later, some of these acquired chemoresistance and once again became a public burden. In view of the protracted course of treatment required with antimonial substances and the frequency of recurrence,¹⁰ one could not deny that this problem was far from being solved satisfactorily. Search for a better form of remedy went on. Every new therapeutic agent, such as the sulfonamide drugs,¹⁰ tyrothricin¹¹ and penicillin,¹² which was found to have an effect on

8 Greenblatt, R. B. Socioeconomic Aspects of Granuloma Inguinale, *J. Ven. Dis. Inform.* **28** 181-183 (Sept.) 1947.

9 Aragao, H. D., and Viana, G. *Mem. Inst. Oswald Cruz* **4** 211 (Jan.) 1912.

10 Allison, G. G. Granuloma Inguinale. A Study of Two Hundred Cases, *J. M. A. Georgia* **35** 103-107 (April) 1946.

11 Greenblatt, R. B., Kupperman, H. S., Dienst, R. B., and Chen, C. H. Unpublished data.

12 Turner, F. B. Granuloma Inguinale. Treatment of Seven Cases with Penicillin, *M. J. Australia* **2** 366-367 (Dec. 1) 1945. Haseick, J. R. A Failure of Penicillin in the Treatment of Granuloma Inguinale, *Arch. Dermat. & Syph.* **52** 182 (Sept.) 1945. Nelson, R. A. Penicillin in the Treatment of Granuloma Inguinale, *Am. J. Syph., Gonorr. & Ven. Dis.* **28** 611-619 (Sept.) 1944.

pathogenic micro-organisms was put on trial. Unfortunately, none of them showed any promise toward the eradication of this dreaded malady and the salvation of these poor sufferers.

Then hope for a better remedy for granuloma inguinale revived when streptomycin was found to be very effective against a number of gram-negative bacteria and fungi which would not yield to any ordinary therapeutic agents. In 1946 we started to treat patients with granuloma inguinale with streptomycin.²² The striking results as seen clinically and microscopically² unequivocally put this substance first in the long list of drugs and methods of treatment for granuloma inguinale.

The treatment of granuloma inguinale with streptomycin required considerable variations in order for an optimal dosage to be established. Accumulated experience has taught us that a daily dose of 2 Gm. or less for even as long as an average of twenty-two days was not ideal. We had 6 recurrences and 2 ultimate failures among 32 patients thus treated. But with the daily dose increased to 4 Gm. the results were manifold, in spite of the fact that the period of treatment was cut down to less than one-fourth. Therefore a sufficient daily dose is probably of primary importance. Since we have had in mind establishing a uniform dosage schedule we have been treating patients with 4 Gm. a day for five days for all early and average cases and for from six to ten days for very extensive cases, regardless of whether or not smear examinations were negative for the Donovan bodies at the end of the course. If the patient had not had any improvement with the ten day course he or she was watched for several weeks to months before being considered resistant to streptomycin. With this regimen we have observed that all those whose smears still showed Donovan bodies at the end of a five day course eventually had complete healing without additional therapy. A specimen taken for biopsy from the healed scar of 1 of these patients was found to be free from Donovan bodies. So far, for a period of eight months the lesion remains healed. Since all recurrences in this series have taken place within the first four months this patient stands a very good chance of becoming permanently cured. Nevertheless this result should not lead us to think that this dosage schedule is as yet standard because there have been 4 patients in whom recurrence was noted in the group treated with the five day course. The fact that all patients treated with the six to ten day course have not had any recurrence probably means that the course of treatment should be increased to ten days at least in cases in which smears are positive at the end of the five day course and in cases with extensive lesions. We feel that by giving sufficient daily and total doses it is possible for one to reduce recurrence to a minimum.

The effect of streptomycin when used in the form of a suppository is apparently greatly decreased. Rectal suppositories, even when given in a dosage as high as 8 Gm per day, were ineffective. Vaginal suppositories seemed to have some effect both locally, as illustrated in the case with the vaginal lesion, and generally, as illustrated in the case with abdominal lesions. But, in view of the rapidity of recurrence in the former and the sluggishness of healing in the latter, in which there was only a very small lesion, use of suppositories should be limited to experimental work.

The treatment of fusospirochetosis before starting treatment of the granuloma with streptomycin, though not essential, is helpful. It enhances the speed of healing of the lesion under subsequent streptomycin therapy by decreasing the exudate which keeps the lesion moist. Dryness is an important environmental factor in the process of healing.

Since both patients who failed to respond and developed resistance to streptomycin thereafter were treated originally with a relatively small dose, it may well be that a small dose is a factor contributing to the development of resistance. Therefore, it is probably essential for one to begin treatment with streptomycin, as with other chemotherapeutic drugs and antibiotics, with a dose large enough to avoid creating resistance. Knop in his experimental study made a similar statement.¹³

The mechanism of the febrile reaction developed soon after the institution of streptomycin therapy is not understood. It has been suggested that it might be a type of the Jarisch-Herxheimer reaction,¹⁴ similar to that encountered in the treatment of syphilis with arsphenamine and penicillin, due to the disintegration of Donovan bodies. There is little reason to account for the absence of involvement of the eighth nerve, except that all our patients were treated with a comparatively short course, the longest of which was sixty-two days, with a daily dose of less than 1 Gm.

Finally, the case of the chemoresistant and streptomycin-resistant patient treated with resin of podophyllum, roentgen radiation and anthiomaline® deserves consideration. We do not think anthiomaline® was responsible for the improvement, for the following reasons:

- (1) Anthiomaline® had been used for months without any significant effect before treatment with streptomycin was begun,
- (2) as a rule, antimonial therapy does not cause such a rapid remission, and
- (3) the stages of improvement did not coincide with the administration of anthiomaline® but ran parallel with the application of resin of podophyllum.

13 Knop, C. Q. Experimental Study of the Development of Resistance to Streptomycin by Some Bacteria Commonly Found in Urinary Infection, *Proc. Staff Meet., Mayo Clin.* **21**: 273-276 (July 24) 1946.

14* Moore, J. E. Personal communication to R. B. Greenblatt.

phyllum While both resin of podophyllum¹⁵ and roentgen radiation¹⁶ have been used successfully in treatment of granuloma inguinale, it is hard to say which of these should be given the credit Judging from the clinical response, resin of podophyllum was probably the chief factor in this case The action of resin of podophyllum on granuloma tissue has been thought to be one of dehydration¹⁵ However, we think its escharotic action was responsible for the results Whether or not it has some specific action on Donovan bodies is a problem requiring further studies

SUMMARY AND CONCLUSIONS

The treatment of 100 laboratory-proved cases of granuloma inguinale with streptomycin is presented in detail, and the proper technic for taking and preparing tissue smears for examination is described

In view of the frequency of improper diagnoses, a laboratory confirmation should be required in every case, and an initial diagnosis should be based on the finding of intramonocytic Donovan bodies

Streptomycin is by far the most effective, if not the ideal, agent in the treatment of granuloma inguinale A specimen taken for biopsy from the healed scar of 1 patient shortly after treatment failed to reveal any Donovan bodies

The optimal dosage for streptomycin is 4 Gm per day, given intramuscularly in divided doses for from five to ten days The ten day course is probably to be preferred, at least in those cases in which Donovan bodies are still present at the end of a five day course and in cases with very extensive lesions With this regimen, toxic manifestations are rare

It is emphasized that streptomycin should be given in sufficient primary doses in order for resistance to this antibiotic to be avoided A preliminary treatment of secondary infections enhances the healing of lesions under subsequent streptomycin therapy

Stilbamidine⁸ (4 4'-stilbenedicarboxamidine) apparently is ineffective in the treatment of granuloma inguinale whereas resin of podophyllum N F is a useful aid Further use of resin of podophyllum is warranted

Experiments conducted along the line of transmission show that granuloma inguinale probably does not develop on normal or simply abraded skin

University of Georgia School of Medicine

15 Tomskey G C , Vickery, G W , and Getzoff, P L Successful Treatment of Granuloma Inguinale with Special Reference to the Use of Podophyllum, J Urol 48:401-405 (Oct) 1942

16 Deibert A V , Greenblatt, R B , Pund, E R., and Cannefax, G X-Ray Therapy of Granuloma Inguinale, to be published

ERYTHEMA ELEVATUM DIUTINUM

Report of Three Cases

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ST. LOUIS

THE NAME erythema elevatum diutinum was used by Crocker and Williams¹ in 1894 to describe a cutaneous eruption in a 6 year old girl. The patient did not have "rheumatism." A microscopic examination of a piece of excised skin showed a fibrocellular structure in the corium but no changes in the blood vessels except a slight cellular infiltration in the outer coats. In 1929 Weidman and Besancon² reported 2 cases of a condition which they described as erythema elevatum diutinum. The name used by Crocker and Williams was retained for the disease, although Weidman and Besancon described histopathologic changes which to them were pathognomonic and did not correspond with those previously described under that name by any other investigator.

Three additional cases presenting this type of histopathologic change have been reported since then: 1 by Combes and Bluefarb in 1940,³ another by Engman, Pfaff and Cooper in 1942⁴ and the third by Ketron in 1944.⁵ Ketron suggested that the number of cases was

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Studies, observations and reports from the Departments of Dermatology of the Washington University School of Medicine and of the Barnard Free Skin and Cancer Hospital.

1 Crocker, H. R., and Williams, C. Erythema Elevatum Diutinum, *Brit J Dermat* **6** 1-9 and 33-38, 1894.

2 Weidman, F. D., and Besancon, J. H. Erythema Elevatum Diutinum. Role of Streptococci, and Relationship to Other Rheumatic Dermatoses, *Arch Dermat & Syph* **20** 593-620 (Nov.) 1929.

3 Combes, F. C., and Bluefarb, S. M. Erythema Elevatum Diutinum. Report of a Case, *Arch Dermat & Syph* **42** 441-446 (Sept.) 1940.

4 Engman, M. F., Jr., Pfaff, R. O., and Cooper, Z. K. Erythema Elevatum Diutinum. Report of Case with Histologic and Bacteriologic Studies, *Arch Dermat & Syph* **45** 334-341 (Feb.) 1942.

5 Ketron, L. W. Erythema Elevatum Diutinum, *Arch Dermat & Syph* **50** 363-372 (Dec.) 1944.

large enough to establish a new entity, emphasizing the microscopic criteria set forth by Weidman and Besancon. He suggested that the name erythema elevatum diutinum be retained temporarily, although the microscopic observations in the 5 cases were not compatible with those described by Crocker and Williams under that title.

We report 3 cases in which the diagnosis of erythema elevatum diutinum was made because of the characteristic microscopic picture seen at biopsy. These changes were essentially the same as those described by Weidman and Besancon. Two of the patients responded to treatment, when last observed they had no cutaneous lesions. The third patient has received no therapy as yet.

REPORT OF CASES

CASE 1—R. B., a 56 year old white fireman, was admitted to the Barnes Hospital on March 8, 1945. The chief complaint was a cutaneous eruption of eight years' duration. This eruption had begun on the feet and then appeared on the elbows, hands, knees and buttocks. In these eight years the eruption had never disappeared, but at times it would fade somewhat, only to reappear. The lesions had never been painful or pruritic, but there had been a "ticking" feeling in them (apparently pulsation). There were no other complaints. The patient had consulted a physician for this eruption in 1935, and a piece of skin had been removed from a lesion of the knee.

The family history disclosed that his mother had had "rheumatic arthritis" for eighteen years and that his father had died of "heart trouble." The patient had had a cough productive of thick, yellow sputum for the three months before admission. There were no neuromuscular complaints.

The examination of the skin disclosed flat nodules and plaques, which were dull red, over the elbows, the dorsal and palmar surfaces of the fingers, the knees, the buttocks, the feet and the ankles. A few of the nodules were arranged in circles or segments of circles. Over the elbows and feet the nodules tended to be discrete. There was some evidence of involuted lesions in that there were brown stains near areas of well developed lesions.

The general physical condition was entirely within normal limits. The red blood cell count was 5,180,000, with 15.2 Gm (98 per cent) of hemoglobin. The white blood cell count was 8,250 cells, with 65 polymorphonuclear leukocytes (33 of which were stab forms), 24 lymphocytes and 11 monocytes. Urinalysis showed nothing abnormal, and the Kahn test for syphilis gave a negative reaction.

The patient's course in the hospital was uneventful. A piece of skin was removed on March 9, 1945, and the patient was discharged on March 10.

The patient was subsequently treated with triweekly injections of 5 per cent casein and 2.5 per cent sodium iodohydroxyquinolinesulfonate (activin®). These injections were continued for six months, the dose being 1 cc, given intramuscularly. The lesions on the buttocks were somewhat recalcitrant and were given a series of roentgen ray treatments, with subsequent complete disappearance of the lesions. Each treatment consisted of 88 r, with 85 kilovolts, 4 milliamperes and an 0.8 mm aluminum half-value layer, with no filter and at a distance of 10 inches (25.4 cm). The treatment with 5 per cent casein and 2.5 per cent sodium iodohydroxyquinolinesulfonate was resumed, resulting in the complete disappearance of the lesions by June 1946. The frequency of administration of the drug, which

had been given three times a week and then twice a week, was reduced to once a week, and when the patient was last observed, in November 1946, all the lesions remained completely involuted, and there was an apparent cure.

Histologic Examination—In a specimen taken for biopsy from a lesion on the knee in November 1935, a small papule about 3 to 4 mm in diameter was included. The epidermis showed relatively little change except for moderate hyperkeratosis and a few small areas of parakeratosis. On the surface of the epidermis in one small area there was a superficial crust made up of fibrin in which leukocytes



Fig. 1 (case 1)—Photomicrograph of the specimen taken in November 1935, showing an early lesion with a very dense cellular infiltrate, made up principally of polymorphonuclear leukocytes, in the dermis.

were embedded, but there was no ulceration beneath it. Although there was moderate acanthosis, the rete pegs were short and stubby. The epidermis as a whole showed intracellular and intercellular edema.

Throughout the upper half of the dermis there was a dense cellular infiltrate made up of large numbers of polymorphonuclear leukocytes together with a few lymphocytes and epithelioid cells (fig. 1). There were several foci in the dermis in which the cells of the infiltrate showed karyorrhexis, but there was no

necrosis The blood vessels were dilated, and their walls were thickened The endothelial cells lining them were hyperplastic, and their nuclei appeared swollen About the vessels was a mantle of eosinophilic, hyalinized, fibrous material which resembled the "toxic hyalin" described by Weidman and Besancon The dermis showed moderate edema

In the specimen removed from the elbow region in March 1945 the changes corresponded to those observed late in the course of the disease by Ketron⁵ and described in his report on biopsy 4 in his case The cellular infiltrate, which



Fig 2 (case 1)—Photomicrograph of the specimen taken in March 1945, showing a relatively late lesion, in which there is a reduction in the amount of cellular infiltrate in the dermis and some fibrosis

tended to be perivascular, was reduced in amount and was made up of polymorphonuclear leukocytes, lymphocytes and epithelioid cells (fig 2) Scattered between the collagen bundles were small basophilic granules, which probably represented fragmented nuclei some of which had been engulfed by phagocytes The blood vessels in this specimen, also, were surrounded by a distinct mantle of hyalinized, fibrous material (fig 3) The dermis was moderately edematous, but early fibrotic changes were present

The changes in the epidermis were minimal and consisted of moderate hyperkeratosis and slight acanthosis, although the rete pegs were shortened and in places almost obliterated. There was some intracellular edema.

CASE 2—N 1, a 59 year old white coal miner, was admitted to the Barnes Hospital on Sept. 27, 1942. The chief complaint was an eruption of the skin of several years' duration and weakness of about three weeks' duration. About two and one-half years before admission the patient had noticed a pruritic itching eruption on the hands, forearms and abdomen. Six months before the present

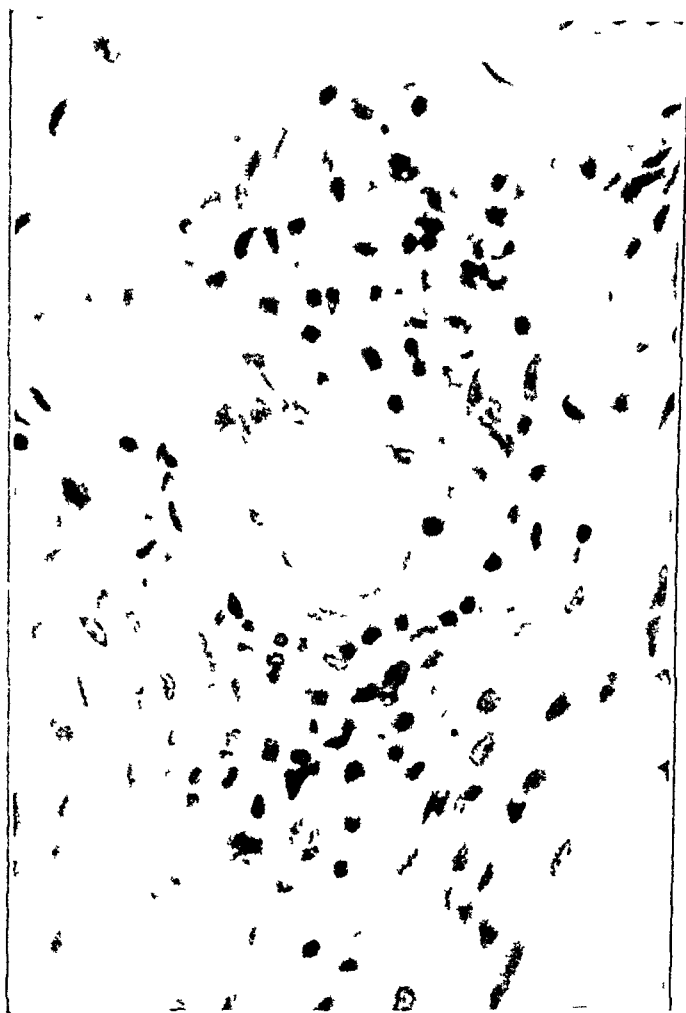


Fig. 3 (case 1)—High power photomicrograph of a small blood vessel in the specimen taken in March 1945. Note the deposit of "toxic hyalin" in the vessel wall and the infiltrate of polymorphonuclear leukocytes and lymphocytes surrounding it.

admission, in a hospital in Illinois, he had been treated for the cutaneous eruption with injections of nitromersol and with sulfathiazole and sulfamidamide, administered orally. The eruption had improved somewhat, but many of the patches persisted.

There was a past history of a slight cough, especially in the winter time, and of occasional fever, related only to a "cold." The patient had never had pains in the joints.

On the dorsal surfaces of the hands, the extensor surfaces of the wrists, the elbows and the area near the suprasternal notch there were dull red to bluish red circular and oval plaques, 2 to 6 cm in diameter. There were a few circinate lesions over the scapulas. Several of the plaques were described as "spongy" to touch, but there was no definite infiltration. The lesions on the backs of the hands were exfoliating slightly. This condition was thought to be due to local applications.

General physical examination revealed a well developed and well nourished white man in no obvious discomfort. All the findings were within normal limits except that the cervical and inguinal lymph nodes were small and firm but not tender. There were pyorrhea and some decay of the teeth. The pharynx was reddened.

The red blood cell count was 4,940,000, with 93 per cent hemoglobin. The white blood cell count was 14,500, and the differential cell count revealed 72 polymorphonuclear leukocytes, 20 lymphocytes and 8 monocytes per hundred cells. The fasting blood sugar was 69 mg, the nonprotein nitrogen 21 mg and the uric acid 3.2 mg, per hundred cubic centimeters. The Kahn test gave a negative reaction. One blood culture was reported as showing no growth. Agglutination reactions for *Eberthella typhosa*, paratyphoid organisms, organisms of the *Brucella* group and *Proteus vulgaris* X₁₀ were negative. The interpretation of the electrocardiogram was indeterminate. The diagnosis based on the roentgenographic examination of the chest was arrested pulmonary tuberculosis of the upper lobe of the right lung and peribronchial fibrosis of indeterminate nature.

The patient's course in the hospital was uneventful except that there was a slight elevation of temperature in the afternoon. The highest temperature recorded was 100 F (37.8 C).

On October 7, 50,000,000 killed typhoid bacilli were injected into a vein. The temperature (rectal) rose to 103.3 F (39.6 C). On October 11, 75,000,000 killed typhoid bacilli were injected into the vein, with a rise in temperature to 100.2 F (38 C). The lesions had improved on October 12. On October 14, 125,000,000 killed typhoid bacilli were injected intravenously, with a subsequent rise in temperature to 102 F (38.8 C). The patient was discharged on October 18. At that time there was involution of all the cutaneous lesions, leaving only slight erythematous and pigmented areas to mark their former sites.

The patient appeared again for observation on November 21, with a few plaques on the backs of both hands. They were treated with roentgen rays at weekly intervals for six weeks. Each treatment consisted of 88 r, with 85 kilovolts, 4 milliamperes and an 0.8 mm aluminum, half-value layer, with no filter and at a distance of 10 inches (25.4 cm). When the patient was examined on March 13, 1943, no lesions could be found. He was seen at monthly intervals up to Nov 27, 1943, and no recurrence was observed.

Histologic Examination—In a biopsy specimen removed in September 1942 from the right supraclavicular area the most striking changes were observed in the dermis. The blood vessels were dilated and the endothelial cells lining them were hyperplastic, but the lumens were not obliterated. About some of the vessels were small deposits of "toxic hyalin," but this change was not as conspicuous in this case as it was in case 1. In the subpapillary portion of the dermis there was a cellular infiltrate made up principally of polymorphonuclear leukocytes, together with some lymphocytes and epithelioid cells (figs 4 and 5). Scattered among the cells of the infiltrate was extracellular basophilic granular material, which probably represented fragments of nuclei. The dermis was moderately edematous.

The epidermis showed hyperkeratosis and was acanthotic. The rete pegs, although relatively regular, were short and stubby.

CASE 3—S. L., a 5-year-old white girl, was admitted to the dermatologic clinic of the Parnassus Skin and Cancer Hospital on Feb. 18, 1941. Her mother had noticed a "pox" on the arm, left buttock, and left leg for eight months. An individual "spot" might fade gradually over a period of several weeks only to reappear in about the same area. The patient stated that the eruption did not itch, although her mother observed that she had scratched a few papules.

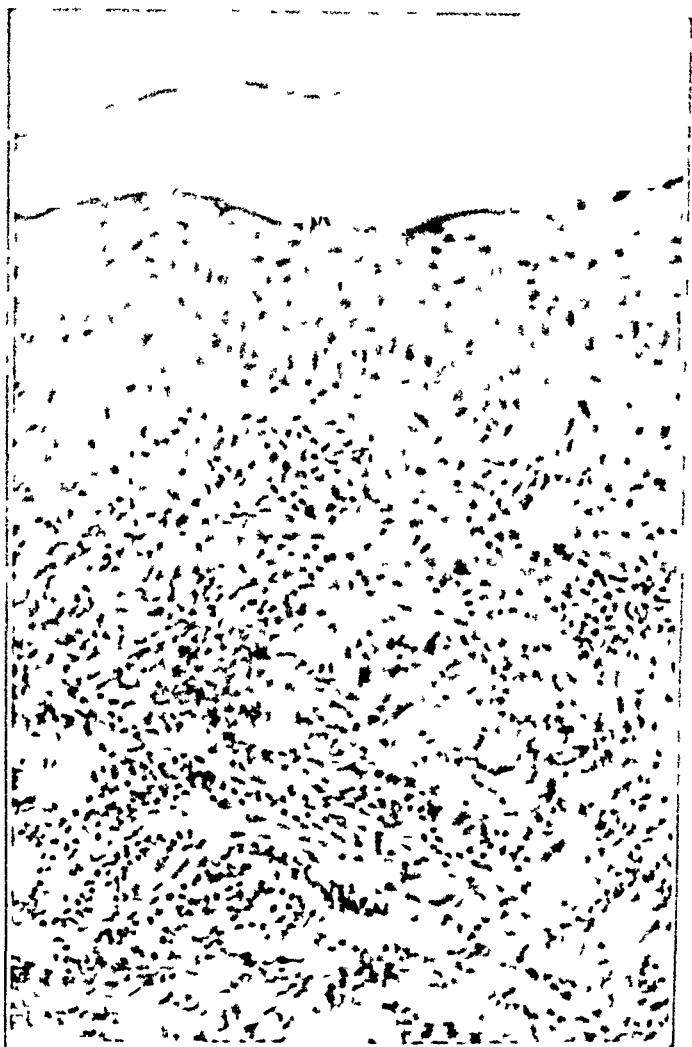


Fig. 4 (case 2)—Photomicrograph of an early lesion, showing a dense cellular infiltrate, in which polymorphonuclear leukocytes predominate, in the dermis.

There was a history of whooping cough at the age of 1 year and measles at the age of 3 years. The patient had been vaccinated and given injections of diphtheria toxoid USP at the age of 1. Her mother and father had been married for twelve years and were both in good health; there were 2 other siblings, aged 10 and 11, and the mother had had no miscarriages. One of the mother's sisters, who had died of tuberculosis, had seen the patient briefly when the patient was 2 years old. The child had no history of pain in the joints or muscular aches.

Examination of the skin revealed a sparse eruption of small (2 to 3 mm in diameter), yellowish brown papules on the trunk, the left arm, the legs and the lower part of the left buttock. There were small inflammatory zones about a few of the papules and a fine grayish white scale over some of them.

The general physical condition was entirely within normal limits. There was no enlargement of the lymph nodes, and the tonsils were very small.

A piece of skin was removed from a lesion of the right buttock on February 18. The patient was treated with local antipruritics, without improvement.

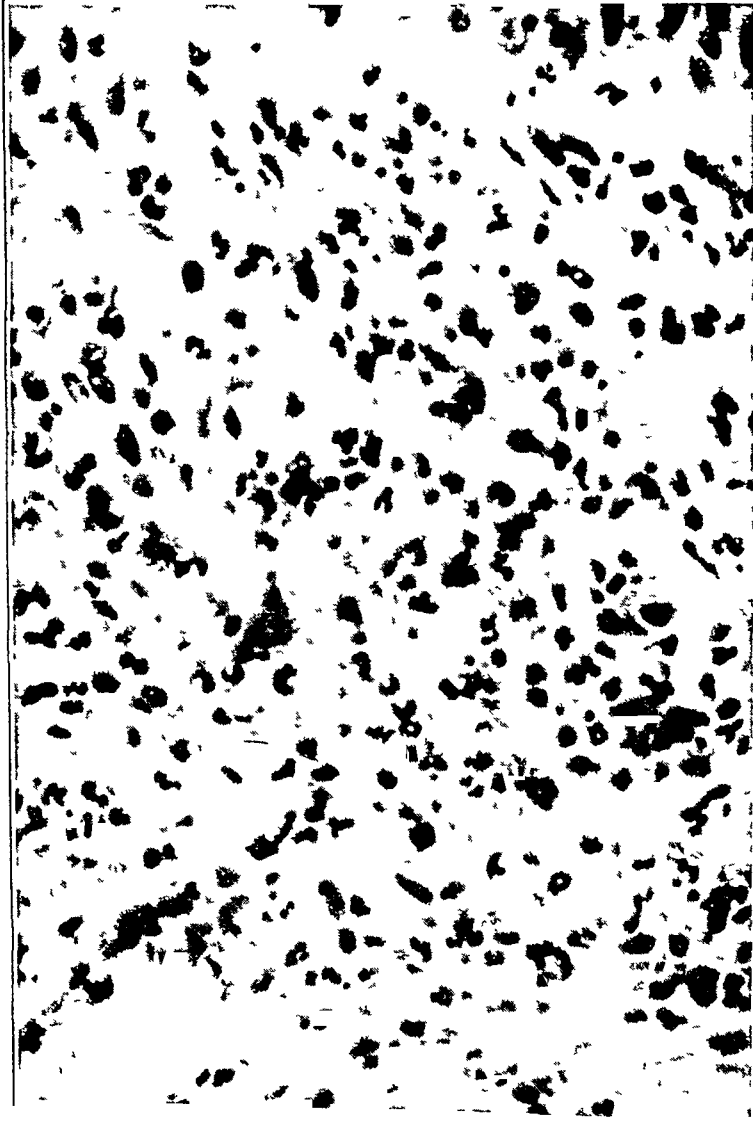


Fig 5 (case 2)—High power photomicrograph of a portion of the dermis, showing the character of the cellular infiltrate. Polymorphonuclear leukocytes predominate.

On Nov 17, 1946 the patient returned to the clinic because the eruption had persisted. The patient's mother stated that there had been some improvement in the cutaneous eruption, especially during the summer months, but that it had never completely disappeared. The patient had been in very good health for the past two years, although she had complained occasionally of "leg aches," which, however, had not prevented her playing out of doors.

An examination of the skin revealed two small (2 to 3 mm in diameter), smooth, yellow brown papules over the left buttock. There was a faint pinkish stain about the old scar at the site of removal of tissue for biopsy, but there were no papular lesions in that area. On the anterior surfaces of the right thigh there was one large, red papule (5 mm in diameter), with a faint pink halo about it. There was a fine, pale yellow scale over the surface of this papule. About this papule were three smaller, brownish yellow ones (2 to 3 mm in diameter).

The general physical condition was essentially within normal limits. The red blood cell count was 4,500,000, with 11.5 Gm. of hemoglobin. The white blood cell count was 8,900, with 54 per cent polymorphonuclear leukocytes, 6 per cent eosinophilic leukocytes, 32 per cent lymphocytes and 8 per cent monocytes. The examination of the urine revealed a specific gravity of 1.025, an acid reaction and no albumin or sugar. On microscopic examination there was normal sediment.

Histologic Examination.—In a biopsy specimen taken in February 1943, the epidermis showed slight hyperkeratosis and moderate acanthosis. The rete pegs were regular in contour but were noticeably lengthened. The epidermis showed moderate intercellular edema.

In the dermis a cellular infiltrate, which was denser about blood vessels, hair follicles and sweat glands, was present. It was made up of polymorphonuclear leukocytes, lymphocytes and epithelioid cells. The walls of the capillaries showed endothelial hyperplasia and about many of them there was a deposit of an eosinophilic toxic hyaline, but the vessels were not occluded. The dermis was moderately edematous.

COMMENT

The histopathologic criteria for the diagnosis of erythema elevatum diutinum as set forth by Weidman and Besancon² are moderate acanthosis in the epidermis and acute toxic periarteritis and peritendinitis in the dermis. Polymorphonuclear leukocytes are abundant about the blood vessels in the dermis, and there is a toxic hyaline degeneration affecting the fibrous tissue about the capillaries. This degeneration is not as extensive as in early lesions but is regarded as characteristic for the disease in the later stages.

In case 1 microscopic examination of biopsy specimens taken ten years apart revealed these characteristic changes. In the earlier specimen a cellular infiltrate, made up predominantly of polymorphonuclear leukocytes, was present in the dermis. The walls of many of the blood vessels showed endothelial hyperplasia, and a zone of "toxic hyaline" was observed about many of them but there was no occlusion of the lumens. In the more recent specimen there was a less dense perivascular cellular infiltrate, in which polymorphonuclear leukocytes were greatly decreased in number. The changes in the vessel walls were similar to those in the earlier specimen, but there was evidence of fibrosis in the dermis. The first specimen probably represents a well developed lesion, and the second, an older lesion.

Microscopic examination of the biopsy specimen taken in case 2 revealed changes similar to those observed in case 1, but less extensive

This specimen presented the picture described by Ketron⁵ as characteristic of an early lesion, a dense cellular infiltrate, consisting mostly of polymorphonuclear leukocytes, endothelial hyperplasia in the blood vessels, and a slight deposit of "toxic hyalin" about some of the vessels

In the third case deposits of "toxic hyalin" are more conspicuous than in case 2, but not so extensive as in case 1. There was a dense perivascular infiltrate in which polymorphonuclear leukocytes predominated. The changes present compared closely with those described by Ketron⁵ in biopsy 2 on his patient, the specimen for which examination he considered to be from a well developed lesion.

The clinical changes in 2 of the 3 patients presented were similar to those in the cases previously reported by other authors. There were more or less persistent, red to purple nodules, with some tendency to grouping about joints. However, an examination of the third patient, the 5 year old girl, revealed only a very few papules over the thighs and buttocks.

The third case was also unusual because of the age at which the eruption appeared. In all the previously reported cases, the patients were more than 30 years old at the time they were studied,⁶ and none of these patients gave any history of the appearance of the eruption in early childhood. Patients 1 and 2 of this report were 56 and 59 years of age, respectively, while the third patient was only 5 years old.

Two of the 3 patients responded well to treatment. They were treated with foreign protein therapy and were apparently cured at the time of the last observation. The third patient has not been treated as yet. Weidman and Besancon noted that the lesions of one of their patients improved after antityphoid vaccination and expressed the opinion that the improvement was due to a nonspecific protein effect. Engman, Pfaff and Cooper used mild foreign protein therapy in their case and noted that many of the lesions disappeared after this treatment.

Barnard Skin and Cancer Hospital

ABSTRACT OF DISCUSSION

DR FRED D WEIDMAN, Philadelphia. I wish first to take this opportunity of giving a follow-up report on the patient of mine to whom Dr Weiss alluded. I have seen the man from time to time, the last time about three months ago. The lesions have regressed to mere areas of pigmentation, and for several years there have been no exacerbations. The patient is still mildly psychotic, and I have always felt that his psychosis had a basis in the general toxemia which he must have, and which is reflected in the histopathologic change in the skin.

It must be remembered that the histopathologic picture alone is not always self sufficient for the establishment of an entity, and in this connection I would

6 Crocker and Williams¹ Weidman and Besancon² Combes and Bluefarb³ Engman, Pfaff and Cooper⁴

cite the nodular perivascularitis reported by O'Leary and Montgomery, with histopathologic changes somewhat similar to those of erythema elevatum diutinum. I believe that minor variations in the tissue reaction should not be given too much weight. I dare say that if, instead of one biopsy, four or five were made on the same patient, there might be as much difference among the pictures presented by them as there is between nodular perivascularitis and erythema elevatum diutinum. In short, the "toxic hyalin" should not be given such weight as to be of itself sufficient to establish an entirely separate entity, but when one adds to that the over-all picture—the progress of the disease, the duration and the gross morbid anatomy—then I think that one is entirely justified in accepting erythema elevatum diutinum as a separate entity.

I did not hear anything said in this presentation about arthritis, such as was present in my 2 cases. Again, I do not think that arthritis is an essential feature of this entity. It is a manifestation of toxemia that is in the picture. It is a part of the case. There is no reason that the joints should be affected in some cases and not in others.

In short, I think that one should be content with looking at erythema elevatum diutinum simply as an expression of a general constitutional toxemia, leaving the scope of the disease large enough to include cases which present the arthritic syndrome.

DR LOUIS H. WINER, Beverly Hills, Calif. In teaching graduate students, I have frequently been confronted with the question "What do you think about erythema elevatum diutinum?"

It has been my opinion that it is an entity closely allied to, if not the same as, granuloma annulare. However, cases have been reported some of which could be interpreted as "knuckle pads" and others as necrobiosis lipoidica diabetorum. I agree with Dr. Weidman that the histologic picture here is not characteristic of any specific disease. The same changes are seen in many diseases of the vessels and also in toxemia.

The histologic sections could have called forth the diagnosis of drug eruption, erythema multiforme or even a mild form of periarteritis or perivascularitis. Therefore I cannot classify erythema elevatum diutinum as a specific histologic entity on the basis of anything shown today.

DR FRANK C. COMBES, New York. I wish to report on a patient I first saw almost ten years ago (Combes, F. C., and Bluefarb, S. M. *Erythema Elevatum Diutinum*, *ARCH. DERMAT. & SYPH.* 42:441 [Sept.] 1940). New lesions have since developed in this case, and the original ones have become progressively larger and firmer. The patient has been treated with roentgen radiation, without the slightest benefit. I have the same results in another case. I therefore am interested in Dr. Weiss's report.

Erythema elevatum diutinum is undoubtedly a clinical entity, independent of granuloma annulare. Unfortunately, when Crocker and Williams wrote an article on this dermatosis, they included a case described by Bury in 1889, which was apparently one of granuloma annulare. Graham Little, in making a survey in 1908, concluded that erythema elevatum diutinum was a subvariety of granuloma annulare, but the cases he collected were mostly of the Bury type. In 1932 Little agreed that the two conditions were distinct, which opinion is generally accepted today.

DR FRANCIS A. ELLIS, Baltimore. Dr. Ketron's patient with erythema elevatum diutinum received roentgen therapy, without any noticeable effect on the lesions.

If one obtained a typical section from a case of fully developed erythema elevatum diutinum trained dermatohistopathologists would be in about 100 per cent agreement on the histologic diagnosis. It is not unusual to see sections in which the picture is that of erythema elevatum diutinum in that there is a fairly dense infiltrate of well preserved polymorphonuclear leukocytes in and about the wall of the blood vessels but not the "toxic hyalin" in the vessel wall. These lesions may represent chronic nonsuppurative pyoderma of the cutis.

DR. RICHARD S. WEISS, St. Louis. In regard to Dr. Weidman's point about the resemblance of this condition to perivascularitis, if both the microscopic picture and the clinical picture are considered, the two diseases can be differentiated. None of our patients had actual arthritis. The little girl complained of growing pains. One of the men patients stated that his mother had had rheumatic arthritis, and he complained of pains in the joints whenever he had a bout of fever.

Dr. Winer, one must consider granuloma annulare in the differentiation of this condition. Blood sugar determinations were made in the cases of the 2 men, but not in that of the little girl, and the values were within normal limits. It is generally accepted that in cases of granuloma annulare the lesions, after they once appear, may disappear for months, and sometimes years, but there are relapses.

Roentgen irradiation. Dr. Combes, was used as adjunct therapy with these patients and was followed up with more protein therapy. The 2 men made an almost complete recovery with residual lesions in some areas, which lesions were treated with superficial roentgen therapy.

One wonders why Dr. Weidman and the other workers took the name of erythema elevatum diutinum for this complex disease, which seems to be entirely different from the eruption described by Crocker. Crocker referred in his article to the previously reported cases which resembled his. I get the impression that the condition in the cases described by Crocker and previous workers were probably granuloma annulare.

I agree with Dr. Ellis that when the histopathologic picture shows the infiltrate consisting of polymorphonuclear leukocytes this complex disease is to be suspected.

HISTOPATHOLOGY OF ATOPIC DERMATITIS AND CHARACTERISTIC ATOPIC REACTION TO PATCH TEST

FRANK A. SIMON, M.D.

AND

A. J. MILLER, M.D.

LOUISVILLE, KY

THE CHARACTERISTIC atopic reaction to patch tests with human dander and the naturally occurring lesions of the disease atopic dermatitis resemble each other grossly in the occurrence of papules, papulovesicles, redness and slight desquamation and in their chronologic development and retrogression. The natural lesions, of course, are frequently modified by trauma and sometimes by secondary infection.

Since the allergen of human dander has been found to be present not only in the scalp but also in the skin of the general body surface,¹ it must be given consideration as a possible clinically important allergenic excitant of the disease. Hence it is desirable to study further, by histologic methods, the similarities and dissimilarities of the natural lesions and the reactions to patch tests.

PRESENT INVESTIGATIONS

Method and Material—This study is based on biopsies made of 14 specimens obtained from 9 patients with atopic dermatitis, aged 6 and 14 months and 5, 5, 6, 8, 14, 15 and 29 years. Sections of natural lesions were removed from all 9 patients. Specimens showing reactions to patch tests were obtained from 5 patients, 3 of the specimens being of patches on normal skin and 2 of patches on scarified skin. The sections of skin were removed with a biopsy punch, fixed in dilute solution of formaldehyde U.S.P. (1:4), stained with hematoxylin and eosin and cut in serial section so that small lesions, such as papules, could be followed throughout their entire course. The dander used for the patch tests was obtained from a normal scalp and mixed with sufficient petrolatum to make a thick paste. The patch remained in contact with the skin for two days, and the sections of skin were removed six hours (in 3 cases), two days (in 1 case) and seven days (in 1

From the Departments of Medicine, Bacteriology and Immunology and Pathology of the University of Louisville School of Medicine.

1. Simon, F. A. The Allergen of Human Dander Present in Skin of the General Body Surface, *J. Invest. Dermat.* **9** 329, 1947; The Allergen of Human Dander—Its Relative Concentration in Several Skin Areas and in Appendages, Products and Derivatives of the Epidermis, *ibid.* **11** 203, 1948.

case) after removal of the patch. Patch tests with egg white, dwarf ragweed pollen, feathers and petrolatum had negative reactions in these 9 patients. In tests on other series of patients, however, reactions similar to those reported here have been produced, in a few cases, by egg white and ragweed pollen.

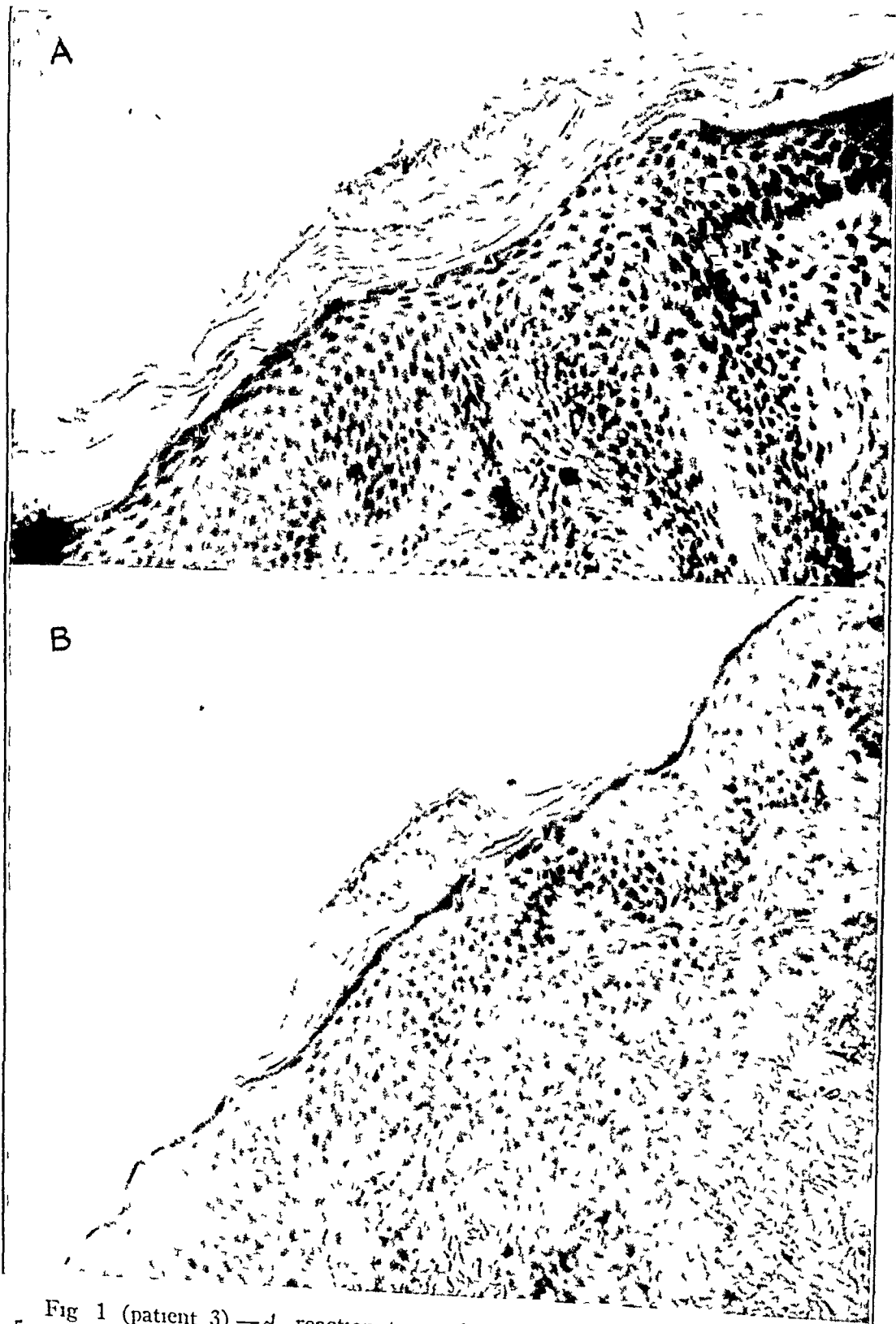


Fig 1 (patient 3) —A, reaction to patch test with human dander in a child 5 years of age. Section was removed nine days after application of the patch. B, natural lesion of atopic dermatitis in the same child.

Results Natural Lesions There were localized areas of parakeratosis in which the stratum corneum was thickened, the cell nuclei were pyknotic, shrunken and irregular in shape. The cytoplasm took the pink stain with eosin and in some areas was vacuolated and granular. In some lesions the surface had a ragged appearance and the surface cells a

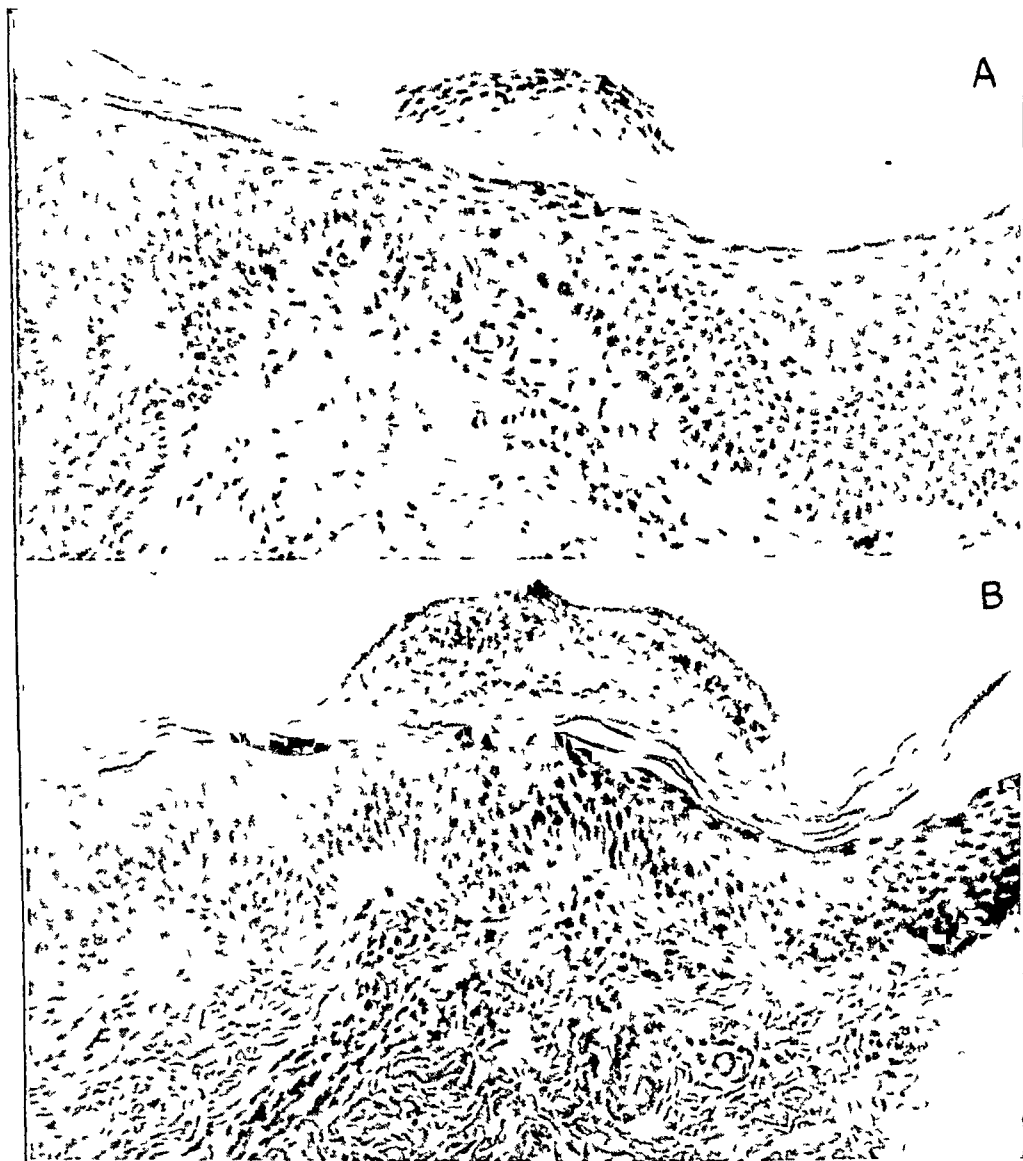


Fig 2 (patient 4)—*A*, reaction to patch test with human dander in a child 5 years of age. Section was removed four days after application of the patch. *B*, natural lesion of atopic dermatitis in the same child.

brownish discoloration. Underlying the areas of parakeratosis the stratum spinosum was, in some cases, edematous and occasionally contained vesicles. An occasional polymorphonuclear leukocyte could be seen in some areas of parakeratosis and also in the stratum spinosum.

In some areas mitotic figures in the stratum germinativum appeared to be more abundant than normal. The underlying dermis was edematous and infiltrated with lymphocytes.



Fig 3 (patient 2)—A, reaction to patch test with human dander in a child 14 months of age. Section was removed four days after application of the patch. B, natural lesion of atopic dermatitis in the same child.

Reactions to Patch Test. The older and less severe reactions showed areas of parakeratosis similar to those described in the pre-

ceding section. The earlier and severer reactions had definite vesiculation of the epidermis. In the case of patch tests on normal, unscarified skin the reactions, unlike the natural lesions, were located in and adjacent to hair follicles and the ducts of sweat glands. In the case of patch tests applied on scarified skin the reaction was located in



Fig 4 (patient 8) —Reaction to patch test in a patient 15 years of age, illustrating an early, severe, acute lesion adjacent to the duct of a sweat gland. Section was removed two days and six hours after application of the patch.

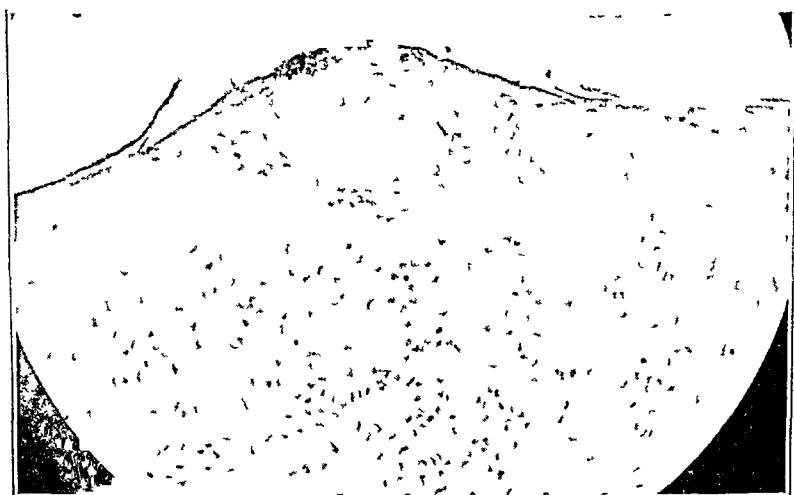


Fig 5 (patient 1) —Natural lesion of atopic dermatitis in a child 6 months of age. This and figure 4 illustrate extreme differences in intensity and chronicity.

the epidermis adjacent to the scratch, regardless of hair follicles or sweat gland ducts. The dermis was edematous and infiltrated with lymphocytes.

COMMENT

The natural lesions and the reactions to patch tests have much in common. They involve the same tissues, with the same type of reaction. That the reactions to patch tests should be somewhat more acute and destructive is to be expected because they are produced by dander from the scalp, which contains a much higher concentration of allergen than the skin of the general body surface¹.

In the case of patch tests applied on normal, unscarified skin the location of the reactions in and adjacent to hair follicles and the ducts of sweat glands may be explained on the basis of penetration of the allergen, which gains entrance to the epidermis most readily through the natural orifices of the skin. The protection from penetration of the allergen afforded by the cornified layer is further demonstrated by the reactions to patch tests applied on scarified skin, in which the lesion occurs in the epidermis adjacent to the scratch regardless of gland ducts or hair follicles, and also by the reactions in hair follicles, which changes are most pronounced in the lower part of the follicle, where the cornified layer is absent, even though this part of the follicle is more distant from the site of application of the patch. In other words, there are slight differences in the location of the reactions and in their intensity and chronicity which may be explained on the basis of variations in the point of application of the allergen and in its concentration. In the natural lesions the allergen may be present, exert its influence and even arise somewhere beneath the surface of the skin. Attempts to identify the allergen in microorganisms cultured from the skin have been unsuccessful². Because of this fact, and also because the allergen has been identified in the epidermis of a newborn infant, we must consider the possibility that it arises in and from the skin itself. In this connection there are two locations in the skin deserving of consideration: locations in which cells are undergoing degeneration. These are (1) the sebaceous glands, which, being holocrine glands, secrete by pushing cells toward the lumen of the gland, where the whole cell degenerates into sebum, and (2) the region of the stratum granulosum and the stratum lucidum, where epidermal cells are degenerating to form the stratum corneum. In both locations, cells are dying, protoplasm is changing chemically and hence there is opportunity for the formation of a "foreign substance" in the body. The slight evidence available from the histopathologic picture points to the stratum granulosum-stratum lucidum area rather than to the sebaceous glands. The question then arises: Can the cells of the stratum lucidum and stratum granulosum be sufficiently dead to produce a foreign allergenic substance and yet

2 Simon, F. A. On the Allergen in Human Dander, *J. Allergy* **15** 338, 1944

sufficiently alive to react allergically to its presence? The deeper reactions in the stratum spinosum may, of course, be due to allergen which has penetrated into this level from overlying layers

SUMMARY

The natural lesions of atopic dermatitis and the cutaneous reactions to patch tests with human dander both show areas of parakeratosis in which the nuclei of epidermal cells are pyknotic, shrunken and irregular in shape and the cytoplasm pink staining and in some cases granular and vacuolated. Beneath some of these areas the stratum spinosum is edematous and in some cases vesicular. The dermis is edematous and infiltrated with lymphocytes.

The reactions to patch tests are somewhat more acute and destructive and are located in and adjacent to hair follicles and the ducts of sweat glands. These differences in the location of the reaction and in its intensity and chronicity are explained as being due to variations in the concentration, penetration and site of application of the allergen.

Heyburn Building (2)

HERXHEIMER REACTIONS IN PENICILLIN TREATMENT OF SYPHILIS IN PREGNANCY

JACK H BOWEN, M D

H N COLE, M D

J R DRIVER, M D

RICHARD C LIGHT, M D

AND

JOHN E RAUSCHKOLB, M D

In Collaboration with M H Gustafson, M D, Burt Held, M D, J M Kam, M D,
Manly Utterback, M D, and A E Walker, M D

CLEVELAND

SINCE October 1943 treatment with sodium penicillin has been carried out in a total of 182 cases of pregnancy complicated by early syphilis at the Cleveland City Hospital and the University Hospitals. Although total doses of penicillin increased as time went on from 60,000 to 9,600,000 units, in the bulk of the cases (86 per cent) at least 2,400,000 units were given in divided doses every three hours for from sixty to one hundred and twenty injections. The results of treatment are measured in terms of the efficacy of penicillin in protecting the fetus or, better, in curing the fetus of the maternal infection.

In this study there were 5 cases of primary syphilis, 63 cases of secondary syphilis and 114 cases of early latent syphilis. Excluded were all cases of patients thought to have had adequate treatment who were re-treated for protection of the fetus, and all late latent cases.

In a study of this kind the value of the results obtained depends largely on follow-up examinations over prolonged periods. By perseverance and unlimited effort, the rate of follow-up examinations on children born to syphilitic mothers was raised from 21 per cent in November 1946 to 96 per cent by May 1947¹. Of the 182 mothers,

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Western Reserve University School of Medicine and under a grant-in-aid from the National Institute of Health, Syphilis Study Section, United States Public Health Service.

¹ Mrs M K Cooney, R N, Mrs Gretchen Jeffery, R N, Mrs Josephine S Watkins, M A, and Dr Gerard DeOreo, Venereal Disease Control Officer, assisted in the observations on these children.

151 had active syphilis, 6 lapsed from observation and 25 are yet to be delivered. The observation period on the child extended over a period of one year before the case was considered closed. Ideally, an attempt should be made to examine these babies monthly for three months, again at six months, and, finally, at one year after birth.

The patients treated early in the series received a crude mixture of penicillin G, F and X containing not more than 100 to 200 Oxford units per milligram. Later, as the product was improved, the concentration rose to from 800 to 1,200 units per milligram. It is important to remember, however, that during the latter half of 1945 and the early half of 1946 the supplies of penicillin contained a high percentage of the K fraction rather than the G, F and X fractions. The K fraction is known to be rapidly destroyed and excreted by the body and thereby is less effective than the G fraction.

CONGENITAL SYPHILIS

Of the 182 cases of syphilis complicating pregnancy, there were 4 cases of congenital syphilis. The mothers of these babies all had acute secondary infections when penicillin therapy was instituted. These 4 cases are presented briefly.

REPORT OF CASES

CASE 1—V L, with a generalized syphiloderm, was treated in the seventh month of pregnancy. She received 300,000 units of penicillin sodium, given in doses of 5,000 units every three hours for sixty injections. Delivery occurred forty-two days later. The mother had an essentially negative serologic reaction one month after delivery. However, the child's blood one month after birth showed rising titers in all qualitative tests, and two months after birth the infant had seroclinical syphilis, with a severe meningeal type of syphilitic changes in the spinal fluid. Nine months later the mother was serologically negative and clinically well and then was lost to further follow-up observation. The child's symptoms responded well to treatment with penicillin, but both mother and child moved out of town seven months post partum.

CASE 2—D W was treated in the sixth month of pregnancy for a papular syphilid. She received 9,600,000 units of penicillin sodium, given in doses of 80,000 units every three hours for one hundred and twenty injections. This penicillin contained a high percentage of the K fraction. The child was born two months after treatment and had a positive serologic reaction of the cord blood. Two months after birth the child's blood showed 16 Kahn units. This reaction persisted, and by the third month snuffles, diarrhea and hepatomegaly had developed. The child was given penicillin therapy and became clinically and serologically free from disease, only to die of pneumonia at the age of 7 months. In the mother in this case, dark field-positive vulvar lesions developed two months after delivery.

CASE 3—E W was treated in her first month of pregnancy for a maculopapular secondary syphilid. She received 1,600,000 units of penicillin sodium, given in doses of 20,000 units every three hours for eighty injections. The child was delivered at term and was clinically well. Ten weeks after birth, the baby's

blood showed 64 Kahn units, and the child had a papular eruption, a nasal discharge, hepatomegaly, splenomegaly and roentgenologic evidence of periostitis of the long bones. The infant was treated with penicillin and was serologically and clinically well on examination seventeen months afterward. The mother, who had been lost to observation until delivery, was found to be seropersistent and was started on long term therapy.

CASE 4—M G, with secondary syphilis, was treated in the third month of pregnancy with 4,800,000 units of penicillin sodium, given in doses of 80,000 units every three hours for sixty injections. This penicillin again contained an excess of the K fraction. When the child was 2 months old, the serologic test showed 64 Kahn units. The infant also had snuffles, hepatomegaly, splenomegaly and rhagades. Roentgenograms of the long bones showed an osteochondritis consistent with syphilis of the bones. The child received a total dose of 550,000 units over a period of two weeks and was completely cured thirteen months afterward. The mother had a serologic relapse nine months after treatment and was placed under standard therapy.

REACTION TO PENICILLIN

The reactions noted in this series of cases were usually minimal. urticaria and febrile Herxheimer reaction. The first may be adequately controlled with diphenhydramine hydrochloride (benadryl hydrochloride®) or tripelennamine hydrochloride (pyribenzamine hydrochloride®), and in no case was it necessary to discontinue penicillin therapy.

However, in 2 cases it is felt that a serious reaction in the form of a placental or fetal Herxheimer reaction occurred, with resulting premature labor and the delivery of a stillborn fetus. Claim has been made that penicillin is innocuous to the child when a pregnant syphilitic woman is treated. Only Ingraham² has raised some question regarding this point.

REPORT OF CASES

CASE 5—C W, in the sixth month of pregnancy, with extensive moist papules and 64 Kahn units, received a total dose of 9,600,000 units of penicillin sodium, 80,000 units being given every three hours for one hundred and twenty injections. She had a grade II Herxheimer reaction. Fetal movements were felt at the onset of treatment, however, after the end of the first day of treatment, neither the mother nor the examining physician was able to detect movement, and no fetal heart tones were heard. Seven days after the end of treatment with penicillin, the mother, who had already gone home after discontinuance of therapy, was delivered of a stillborn fetus.

CASE 6—The case of B K was similar. She was in her seventh month of pregnancy and had an extensive syphiloderm with dark field-positive moist papules, despite the fact that she had had eight intravenous treatments with penicillin, given irregularly by her family physician, the last one only three weeks previously. She received 9,600,000 units of penicillin, given in doses of 160,000 units every three hours for sixty injections. Her temperature rose from 36.8 to 37.8 C (98.2 to 100 F) and dropped in three hours to 36.8 C. She complained of absence of fetal movements after twenty-four hours, and examination revealed absence of

² Ingraham, N R, Jr. Penicillin Treatment of the Syphilitic Pregnant Woman, J A M A 130 683-688 (March 16) 1946

fetal heart tones The patient left the hospital on the eighth hospital day and was admitted to the delivery room in another hospital ten days later, at which time she was delivered of a macerated fetus

In neither case was it possible for us to get an examination of the dead fetus

SUBSEQUENT PREGNANCIES IN PENICILLIN-TREATED SYPHILITIC MOTHERS

Another interesting feature of this series of cases is that of the mothers who were treated for syphilis with penicillin either during a previous pregnancy or at some time before the inception of pregnancy Each of 7 mothers who were treated for early syphilis in one pregnancy had a normal child in a subsequent pregnancy without benefit of additional treatment In 6 of our cases the mothers became pregnant after treatment with penicillin for various stages of early syphilis and were delivered of normal babies without further treatment

Despite these 13 cases in which previous penicillin therapy apparently protected the baby in a subsequent pregnancy, the question arises as to what should be the practice concerning a pregnant woman with a history of syphilis

Throughout this study are instances in which the penicillin cured the syphilis in the child and yet the mother later had a relapse This result occurred in 44 of 151 cases, and there are 25 recent cases in which the mother is yet to be delivered In many of the 44 known cases of relapse, penicillin in small doses was being employed, and, too, in some of these cases penicillin with a high proportion of the K fraction was being used

Since penicillin therapy is a comparatively innocuous procedure, it is our feeling that in all cases of pregnancy complicated by a syphilitic infection, even though treated, the mother should have a course of treatment with penicillin This would not necessarily require hospitalization, for such a mother could easily be treated in an ambulatory fashion by a semiweekly intramuscular injection into alternate buttocks of 600,000 units of one of the crystalline penicillin compounds in an absorption-delaying base The initial dose should be small, and the total dosage, four to six injections

SUMMARY AND CONCLUSIONS

A series of 182 patients with early syphilis complicating pregnancy were treated with varying doses of penicillin sodium Twenty-five of these patients have not yet been delivered, 6 have lapsed from observation, and 151 had active syphilis

Four children were born with congenital syphilis in this group of 151 mothers with active syphilis

An efficient follow-up procedure is a *sine qua non* in a clinic for "syphilis in pregnancy" Through great effort, it was possible for the

clinics represented in this study to raise their percentage of follow-ups within a period of nine months from an active average of 21 per cent to an active average of 96 per cent

Penicillin seems to be almost a specific drug for syphilis in pregnancy, so far as the child is concerned, as may be seen from the reported results of only 4 cases of syphilitic children of the total of 151 cases of active maternal syphilis analyzed

It is our feeling that in the present status of penicillin therapy it is advisable to treat the syphilitic woman in subsequent pregnancies, regardless of the physical and serologic findings. After all, penicillin therapy is a comparatively innocuous procedure

In view of the large number of mothers 44 of 151 patients who relapsed after delivery, frequent follow-up examinations of these women are essential. It is recommended that monthly examinations and titered blood tests be made until the patient has been serologically and clinically well for one year

Two cases are presented of patients who were thought to have had serious fetal or placental Herxheimer reactions. In each instance fetal movements and a fetal heart tone present before treatment was started ceased within twenty-four hours after the institution of penicillin therapy. It is strongly felt that the dose of penicillin for the first twenty-four hours should be kept low, extremely low, to prevent such an occurrence

Clinical Notes

INCIDENCE OF PSORIASIS

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The incidence of psoriasis among the population at large was calculated by Gahan¹ at "not less than 10 per cent of the people living in and around New York." The basis for his figure was the fact that approximately 700 new cases of psoriasis were seen annually at the New York Skin and Cancer Unit. He estimated that "probably the Skin and Cancer Unit received no more than 10 per cent of the total number of patients who go for treatment to the various clinics in the New York Metropolitan Area," but he allowed, in arriving at a rough estimate, that even if that clinic received even as much as 20 per cent, "this would indicate a minimum figure of 100,000 for the number of persons suffering from psoriasis in and around the city of New York, an area containing approximately 10,000,000 population."

The Army General Hospital in the Zone of the Interior, where dermatologic service was supplied by me to both inpatients and outpatients, constituted a community of men of military age among whom it may reasonably be presumed that I saw every case of psoriasis. In the ten months from August 1943 to May 1944 there were 4,732 patients admitted to the hospital who were not admitted to the skin section. Of these, 10 persons, or 0.2 per cent, had psoriasis. There were in addition 201 patients admitted to the skin section, and of these, 3, or 1.5 per cent, had psoriasis. Army personnel of the detachment serviced by the dispensary comprised altogether approximately 1,000 persons, of whom 3, or 0.3 per cent, had psoriasis.

Psoriasis, accounting for roughly 1.5 per cent of cases of Army personnel hospitalized because of dermatoses, was far down on the list of common diseases of the skin, in contrast to its position second only to acne in order of frequency in the list of Bereston and Ceccolini,² whose report concerned dermatoses in 20,000 inductees. Psoriasis was found in only 0.2 per cent of persons, either hospitalized or on duty, who may be considered a random sample of the Army population.

CONCLUSION

Gahan's figure of "not less than 1 per cent" is too high an estimate of the incidence of psoriasis, and 0.2 per cent is a figure more nearly approximating the truth.

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* Formerly Major, Medical Corps, Army of the United States, Chief of Section on Skin and Syphilis, Woodrow Wilson General Hospital, Staunton, Va.

1 Gahan, E. Incidence of Psoriasis Among the Population at Large, Arch Dermat & Syph **48** 305 (Sept) 1943.

2 Bereston, E. S., and Ceccolini, E. M. Incidence of Dermatoses in Twenty Thousand Army Induction Examinations, with Note on Syphilis with Negative Serologic Reactions, Arch Dermat & Syph **47** 844 (June) 1943.

STREPTOMYCIN OINTMENT IN TREATMENT OF SYCOSIS VULGARIS

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HONOLULU, HAWAII

Several months ago a former patient wrote to me regarding the cure of his recalcitrant sycosis vulgaris. This condition had been refractory to all topical medications, including penicillin ointment, quinolor® ointment,¹ ammoniated mercury ointment and wet dressings of tyrothricin. An ophthalmologist had casually mentioned that streptomycin ointment might be tried, as it had been successful in treatment of staphylococcic marginal blepharitis. In seven days the patient's skin was entirely clear, and it has remained so for six months at the time of writing.

An ointment containing 1,000,000 units of streptomycin powder per ounce (28 Gm) of carbowax 1540® was used. This was vigorously applied before and after shaving and again at bedtime. Fifteen patients with sycosis vulgaris were treated. Duration of infection varied from two weeks to nine months. Cultures of infected hairs produced *Staphylococcus aureus* and *Staphylococcus albus*. In 12 cases there were good results, with clearing in from ten to twenty days. Itching usually subsided within the first week. No relapses were noted in three months. In 2 cases the patients had relapses after ceasing the streptomycin inunctions but remained free from symptoms while using the ointment. No cases of sensitization were noted in this small series.

Each patient was warned about the possibility of present and future allergic sensitization and about developing resistance to streptomycin. A recent report² demonstrated the possible epidermal sensitizing effect of the drug. Most of the patients previously had used many medicaments and were willing to take the risk of sensitization.

This antibiotic certainly is not the complete answer to this stubborn follicular infection, but it is suggested that it can be used as another helpful medicament in the therapeutic armamentarium.

1 Quinolor® compound ointment consists of equal parts of white petrolatum and wool fat, containing 10 per cent benzoyl peroxide and 0.5 per cent quinolor® (a mixture of 3 chlorine derivatives of 8-hydroxyquinoline).

2 Rauchwerger, S M, Erskine, F A, and Nalls, W L. Streptomycin Sensitivity. Development of Sensitivity in Nursing Personnel Through Contact During Administration of the Drug to Patients, *J A M A* 136:614-615 (Feb 28) 1948.

ANTITHYROID AGENTS

Use in Treatment of Dermatitis Herpetiformis, Iododerma and Deep Mycotic Infection

THEODORE CORNBLEET, M D
CHICAGO

Recently certain synthetic materials have been found that oppose the formation of thyroxin, the active principle of the thyroid gland. This newer group consists of a number of substances, of which thiouracil and propylthiouracil have become the best known. The action of the thyroid gland is intimately connected with the metabolism of iodine since this element is utilized by and in a

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sense serves to regulate the action of this endocrine structure. It was natural, therefore, to wonder whether the new antithyroid agents would affect dermatologic entities that are influenced by iodides.

Accordingly, 4 patients with dermatitis herpetiformis were treated with propylthiouracil¹. They were given 100 mg (2 tablets) three times a day, for ten days for 3 of the subjects and for seven days for 1. At the end of this time none was improved. One of the 3 had more lesions and complained of increased pruritus. The treatment of the fourth patient was interrupted at his insistence because of excessive itching. There were no untoward results otherwise. One patient who seemed to be uninfluenced clinically showed a drop in leukocyte count from 7,400 to 3,950, and the man who refused to continue after seven days of treatment because of increased itching had an increase of eosinophils from 2 to 9 per cent.

One patient with an acneform iododerma profusely distributed on the trunk and some lesions on the face was given a trial with propylthiouracil. She used 100 mg (2 tablets) three times a day for eight days. There was no evident improvement in the eruption, nor was there any untoward reaction. Her urine at the end of this period still gave a strong qualitative reaction for iodides.

An opportunity is being awaited for a trial of propylthiouracil in treatment of a person with a deep mycotic infection who shows no favorable response to iodide therapy.

1 The propylthiouracil used was supplied by Eli Lilly Co., Indianapolis.

Society Transactions

DETROIT DERMATOLOGICAL SOCIETY

James R Rogin, M D, *Chairman*

Hermann Pinkus, M D, *Recorder*

Nov 20, 1946

All cases were presented by DR UDO J WILE and DR ARTHUR C CURTIS

A Case for Diagnosis (Poikiloderma?) in a Boy Aged 15 Years

Xanthoma Tuberosum Multiplex in a Boy Aged 28 Months (One of Triplets, the Only One with the Disease).

Disseminated Sporotrichosis

R F, a white man, aged 70, first noted an erythematous papule on the lower part of the back which became fluctuant and discharged purulent material about the middle of September 1946. Two more similar lesions developed within a few days—one on the right thigh and another on the right temporal region. He was given sixty-six injections of penicillin, during the course of which a widely disseminated eruption developed, consisting of red, slightly tender, furuncle-like lesions which discharged seropurulent material and cleared after a few days, only to be succeeded by new similar lesions.

The patient had no knowledge of an injury at the site of the first lesion. He had an epithelioma on the right cheek several years ago, which was treated by means of roentgen rays in another hospital.

The patient did not appear acutely ill. The eruption consisted of widespread, discrete, erythematous papules and papulopustules, varying in size from that of a green pea to that of a half-dollar. Some of these had ruptured and were covered with a crust. They were only slightly tender. The soft tissues of the right great toe, left forefinger and right fifth finger were swollen, red and tender to pressure.

Results of routine examinations of urine and blood were normal. The Kahn reaction of the blood was negative. Results of sternal marrow examination were interpreted as indicative of malignant reticuloendotheliosis. Numerous biopsies of cutaneous lesions demonstrated "mixed tuberculous and pyogenic granulation tissue." Cultures grown from three widely separated lesions showed a pure culture of *Sporotrichum schenckii*. The patient was treated with potassium iodide by mouth.

DISCUSSION

DR ARTHUR SCHILLER: I wonder in cases of this kind why blood cultures should not show organisms and why there is no pulmonary or other organ involvement? I do not believe that the lesion on the face is the same as the lesions on the body.

DR HARTHER KEIM: I wondered about the possibility of a disseminated deep fungus infection. Some of the other lesions which were partially ulcerated sug-

gested sporotrichosis, but I have never seen a disseminated type of the disease before

DR UDO WILE I saw this patient when there were large tumors along the arms which closely resembled abscesses. The pathologists offered little in the way of information. It was diagnosed as tuberculosis but could not have been this. All the larger growths have disappeared with treatment. The finger lesions have healed. All involvement is not only that of soft tissue, but the roentgenograms show bone changes in both the right index finger and the right first toe. This is a unique case of sporotrichosis.

DR HERSCHEL ZACKHEIM (by invitation) I have found that serial dilutions of Sabouraud's 4 per cent dextrose broth containing concentrations of streptomycin as high as 256 units per cubic centimeter failed to inhibit the growth of *Sporotrichum schenckii*.

DR EDWARD CAWLEY (by invitation) The cultures from the lesions of this man were planted, and for several days nothing was seen. The day he was ready to go home, the growths were large enough to be of significance. Dr Schiller spoke of blood cultures. We had no opportunity to do these because we did not find that he had sporotrichosis until too late. Lewis and Hopper (*An Introduction to Medical Mycology*, Chicago, The Yearbook Publishers, Inc., 1938, p. 168) described a subcutaneous disseminated type of sporotrichosis, apparently this disease occurs in France with a fair degree of frequency but is extremely rare in this country. This man has a pulmonary lesion, the nature of which was not clarified by the roentgenograms.

Generalized Progressive Scleroderma

H. J., a white woman aged 42, was first seen at the University Hospital in October 1941, with the complaint that during the previous eight months she had had swelling and muscular pain and tenderness of her extremities. An increased sensitivity to heat and cold had also been noted, and the hands had recently shown cyanotic tendencies in cooler temperatures. Edema of the face, which appeared from time to time, was also mentioned by the patient. The examination here demonstrated little more than the fact that application of external heat to the hands and feet caused vascular dilatation. The digits were described as "cold, wet, thickened and mildly edematous." Muscular weakness and tenderness were found greater in the right than in the left extremity. Hyperesthesia and increase of reflexes were also more pronounced on the right. Pigmentation in the few areas exposed to light was excessive. Laboratory observations were normal at that time, and results of biopsy of skin and muscle taken from the calf were inconclusive. The patient left our care but returned in February 1946. The disease had gradually progressed, and she then complained of intense pruritus together with fixation of the skin, not only of the extremities but also of the face, with some difficulty in swallowing. Pigmentation had become extensive and pronounced.

In childhood the patient had had diphtheria and scarlet fever. At 18 years she had had pleurisy. At 27 a hysterectomy with a left oophorectomy was performed, and at 33 a gastric stricture was relieved surgically. The family history was not contributory.

Almost the entire integument was involved by a mottled brown-gray pigmentation. The skin of the extremities and neck was particularly hidebound and thickened. There was some facial restriction of motion, particularly about the mouth. A few urticarial papules and excoriations were seen on the extremities. The Kahn reaction of the blood was negative.

The patient was given a long regimen, consisting of ammonium chloride, 6 Gm in three day courses, with three days of rest between courses. Diphenhydramine hydrochloride (benadryl hydrochloride®), 200 mg daily, was also administered. By August 1946, the patient reported increased motility of the arms and greater laxity of the skin about the face. The skin on the extremities and face was objectively much less hidebound. Many more excoriated papules were seen about the back, abdomen and wrists. Benzyl benzoate lotion was prescribed, with complete relief from the itching.

DISCUSSION

DR ARTHUR SCHILLER I should like to ask Dr. Curtis whether he is of the opinion that diphenhydramine hydrochloride (benadryl®) is superior in treatment of this disease?

DR ARTHUR CURTIS The patient is receiving ammonium chloride, 6 Gm for three days followed by omission of the drug for three days, and she is also receiving benadryl®. In scleroderma an early change in the skin is a deposit of calcium. In later stages this may produce calcinosis. In an attempt to decalcify the skin ammonium chloride is given, as mentioned before. Many of these patients have said that they have some softening of the skin. The Mayo Clinic is using benadryl® in the treatment of scleroderma. I cannot say with certainty whether or not any of this woman's improvement is due to benadryl®.

DR JAMES ROGIN One year ago, Dr. Paul O'Leary was using benadryl® in the acute edematous stages.

DR HERSCHEL ZACKHEIM (by invitation) At Receiving Hospital 1 patient with advanced scleroderma was given benadryl®, 480 mg daily for over three months, with no noticeable improvement.

A Case for Diagnosis (Ehlers-Danlos Syndrome and Lupus Erythematosus?).

Linear Nevus (Ichthyosis Hystrix)

Atrophoderma Maculatum (Anetoderma of Schweninger and Buzzi)

Tuberculosis Luposa.

L. P., a white man aged 28, was well until seven years ago, when he noted a swelling in the anterior portions of the neck, this was incised, resulting in a discharging sinus. Since that time similar lesions have appeared on the neck and ankles. In 1943, he noted a crusting eruption on the face, which became more extensive, produced considerable scarring and persisted, despite sanatorium care. Development of a carcinoma in an old scar on the nose resulted in amputation of the nose a few years ago. The family history is not significant.

Examination of the face some months ago showed a crusted and ulcerated eruption, with extensive scarring. Apple-jelly nodules were apparent on diascopy. Pigmented scars were present at the suprasternal area and on the ankles.

Results of blood cell counts and urinalyses have always been normal. Repeated roentgenograms of the chest have been normal. The Kahn reaction of the blood was negative. At least one of several biopsies of the face demonstrated tuberculous granulation tissue. For several months the patient has received 300,000 units of vitamin D each day with decided improvement of the face.

DISCUSSION

DR UDO WILE This man has lupus vulgaris. He has an amazingly long history of the disease. Three years ago he had a small lesion on the nose which was erroneously diagnosed in the laboratory as carcinoma. The nose was ablated. Three months ago he had numerous tuberculous nodules on the face and a large ulcerated tuberculous lesion at the angle of the mouth. He was given 300,000 units of irradiated ergosterol and 6 Gm of calcium gluconate daily. The lesions have all healed. This is the second case I have had, with the same amazing results. Successful treatment of lupus vulgaris with vitamin D was the outstanding dermatologic achievement to come out of Europe during the war.

DR ARTHUR CURTIS About three years ago the patient had his nose ablated, yet I feel sure that the changes were those of pseudoepitheliomatous hyperplasia and not epithelioma. His disease was so extensive that a diagnosis of leprosy was made in one of the state sanatoriums.

DR LOREN SHAFFER The question of the joint use of calcium with irradiated ergosterol arises. There is a theoretic possibility of one's producing calcinosis by such joint use. The English are not using such a combination. Since you have recently been in Europe, Dr Wile, I wonder whether you have any further opinion.

DR UDO WILE I can only judge from the French experience, since they are using both, and with good results.

DR ARTHUR CURTIS It is known that irradiated ergosterol mobilizes calcium from the bones. Even though the patient was getting large doses of vitamin D, his blood calcium rose only to levels of 10.5 to 12 mg per hundred cubic centimeters. High levels like this are not in the least dangerous.

Multiple Idiopathic Hemorrhagic Sarcoma**Poikiloderma Atrophicum Vasculare****Cushing's Syndrome with Hidradenitis Suppurativa**

M. P. was a white woman aged 48. In 1931, this patient's menstrual flow became scanty, and she noticed a decided increase of bodily hair and the growth of a beard. A short time later, painful furuncle-like lesions developed at the sides of the nose and in the axillae, groins and gluteal cleft. During subsequent years she has continued to have lesions at the sites mentioned, and bodily hair growth has become excessive, necessitating, on the face, daily shaving. The family history is not significant.

Examination showed hypertrichosis of the face, back and chest. Lesions of hidradenitis suppurativa are present on the face and breasts and in the axillae and perineal regions. The blood cell count was normal with the exception of 16,000 white cells. The differential count was normal. The Kahn reaction of the blood was negative. The basal metabolic rate was plus 13 per cent. The result of the glucose tolerance test was normal. The rate of 17-ketosteroid excretion was 14.1 mg per day. Roentgen examination showed a diaphragmatic hernia, minimal osteoporosis of the spine, calcification of a uterine fibroid and a normal skull. Excretory pyelograms showed no evidence of an adrenal tumor.

DISCUSSION

DR HENRY BRUNSTING In many patients with hidradenitis suppurativa there is usually associated acne of the face and back. I have always felt that there may

be some type of endocrine disturbance in these patients, however, I have never observed the association of Cushing's syndrome previously. Surgical measures, such as excision of the entire hairbearing area of the axilla followed by a full thickness graft should not be postponed too long. After this procedure I have seen other areas of involvement, such as the groin, improve spontaneously.

DR ARTHUR CURTIS I was glad to hear Dr Brunsting make these statements, and I agree with what he says. I feel certain that this patient has a basophilic adenoma of the pituitary or Cushing's syndrome. She has a prominent hump of fat on the upper part of the back as well as decided hirsutism. Her blood pressure is slightly elevated and her bones slightly decalcified. The basal metabolic rate is also increased. No glycosuria is present, and there are no striae. She is 49 years old, and her condition came on suddenly. Roentgenograms of her sella turcica showed no pathologic changes, which is not uncommon. She was studied by Dr Conn, the endocrinologist, who agreed with the diagnosis of Cushing's syndrome.

James R Rogin, M D, President

Hermann Pinkus, M D, Recorder

Jan 15, 1947

All the cases except the last two were presented by Dr Frank Menagh and Dr C E Reyner.

Mycosis Fungoides with Ulcerated Granulomas and Psoriasiform Plaques.

Five Cases of Tinea Capitis with Apparent Satisfactory Response to Treatment with Ointment of Copper Undecylenate

DISCUSSION

DR J H WELCH (by invitation) We have treated 12 patients with tinea capitis diagnosed by the Wood light but not by culture studies with an ointment containing copper undecylenate. Of the 12, 5 apparently have been cured (by the Wood light examination). The period of treatment has ranged from four months to three weeks. Nearly all had had previous treatment without effect. Three or four had epilation by roentgen rays. Of the 5 patients cured, 3 had not been treated by epilation and 2 had. We regard this as a fairly effective agent for handling the type of infection under discussion.

DR LEE CARRICK At the City of Detroit Receiving Hospital we have had some success with an ointment containing undecylenic acid, zinc undecylenate and sodium tetradecyl sulfate, a wetting agent (Carrick, L. *Methods of Local Therapy for Tinea Capitis Due to Microsporum Audouini*, *J A M A* **131** 1189-1194 [Aug 10] 1946). With the undecylenic acid-zinc undecylenate preparation, used according to certain specific directions and in conjunction with a soap substitute, we were able to cure 40 per cent of 25 outpatients over an average treatment period of four and a half months. An additional 32 per cent were cured after a longer treatment period, bringing the total incidence of cures to 72 per cent.

DR ARTHUR SCHILLER I have been interested in the treatment of ringworm by various types of chemotherapy. We started with a copper oleate ointment, and the U S Public Health Service found in their Hagerstown experiment that copper oleate gave 37 per cent of cures. We then devised a copper propionate, and in the Hagerstown experiment this stood third in the list of drugs which gave relatively adequate results in ringworm treatment.

In our opinion, the results depend largely on the type of base in which the medicament is dispensed. In the Hagerstown experiment the first preparation on the list was salicylanilide ointment, which was credited with 57 per cent of cures. In the past seven months our results show only 46 per cent cures. Most of the treatments seem to effect improvement up to a certain point. Occasionally, when small stubborn patches are encountered, removing the hair with a standard barium sulfate paste seems to speed up the cure. Needless to say, the diagnosis should be checked by microscopic examination and culture.

DR LOREN SHAFFER At Wayne University Medical School we have worked with a grant from the Children's Fund of Michigan on this study. We have not got far beyond what you have heard. Not enough consideration is given to prevention of infection in other members of the family when one child has an infection of the scalp. I feel that the application of any unsaturated fatty acid once a week would be effective in prevention and might be used in the schools. It is felt that tincture of green soap, or any soap, should not be used daily. Using a strongly alkaline soap neutralizes the effect of treatment—removes the chemical preparation and the acid reaction. My advice is to use a soap substitute with a low p_H value.

DR HERMANN PINKUS I realize that the situation in a small town is different from that in a large city like Detroit. In Monroe, Mich., a town of 20,000, we had an epidemic of approximately 150 cases in the winter of 1945-1946. Fortunately, the cases were confined almost entirely to one part of the town, in one public and one parochial school. There was fine cooperation from all authorities. All the children in the schools were checked systematically and repeatedly with the help of filtered ultraviolet rays, and infected children were kept out of school unless they were under medical care. During the height of the epidemic special classes were instituted for the patients. Most of the children were treated by roentgen ray epilation followed by antiseptic ointments. In several instances in which the parents did not agree to roentgen treatment at first or in which general practitioners handled the cases, the parents eventually asked for roentgen ray epilation when they saw the poor results of local therapy. When the schools reopened in the fall of 1946, the school authorities checked all the children within the first few weeks. Only a few patients with tinea capitis were discovered, and most of these had moved into town from other places during the summer.

DR ARTHUR SCHILLER I do not like to discourage Dr. Pinkus' optimism as far as the disappearance of ringworm in Monroe is concerned, but we have noticed a reduction in the number of cases in Detroit. In other sections of the country workers also have noticed a lessened number. I think that probably there is a certain degree of immunity established, but I am not at all convinced that another summer will not see a recrudescence of ringworm.

Herpes Zoster with Ramsey Hunt's Syndrome

Sudek's Atrophy of the Right Hand Following Herpes Zoster

M. V., a man, aged 60, was hospitalized in July 1946 with virus pneumonia, and after this herpes zoster of the right arm and hand, extending to the scapula, developed. There was much swelling of the fingers, with tenderness and inability to make a fist.

The vesicles appeared on the fingers of the right hand, up the anterior part of the forearm and the inner aspect of the arm to the scapula, in the

distribution of the fifth, seventh and eighth cervical nerves. The pain continued, with the patient unable to use the right hand. On Oct 25, 1946, roentgenograms showed osteoporosis of both hands and wrists, most marked on the right. There was some atrophy of the muscles of the arm, weakness and fibrillary twitching. The fingers were painful, and the hand could not be closed.

There was osteoporosis of the right hand, with a worm-eaten appearance different from the diffuse osteoporosis of the left and characteristic of Sudek's atrophy.

Roentgen treatment of the involved ganglions, twenty intravenous injections of 100 cc of 10 per cent sodium iodide and sedatives were given and had little effect on the course of the pain and disability. However, immediate improvement was experienced with the injection of tetraethylammonium chloride, 10 cc of which was given twice daily for three days. There was no notable drop in blood pressure, and the improvement has continued. The swelling and the increased perspiration have disappeared.

DISCUSSION

DR DANIEL BUCHANAN (by invitation) Sudek's atrophy is a condition in which, after an injury such as a fracture or sprain, there are severe pain and redness of the extremity and changes in the bone. The bone becomes mottled and decalcified. The bone picture alone is not diagnostic. It is seen also in many cases of fracture incurred in the war which required long immobilization. The disease is thought to be due to autonomic stimulation with vasodilatation, anoxia and further reflex stimulation of nerves and production of changes in the tissue. If you can break the cycle, you can cure the patient. One investigator used tetraethylammonium chloride with considerable success.

DR ARTHUR SCHILLER I should like to ask what benefit you have had from large doses of thiamine given intravenously.

DR FRANK MENAGH We have not used it recently. A few years ago, we treated a series of patients but were not impressed with its value.

DR HERMANN PINKUS I noticed that one of these men gave blood to another patient with herpes zoster.

DR FRANK MENAGH Dr Trygve Gundersen found that if you give a blood transfusion early in herpes zoster ophthalmicus you can prevent damage to the cornea. (Convalescent Blood for Treatment of Herpes Zoster Ophthalmicus, *Arch Ophth* 24 132-141 [July] 1940) I do not know that I ever saw a case of Bell's palsy clear up as rapidly as this.

Melanosia (Riehl's?); Hyperpigmentation of Face and Arms

Chronic Intercrural Dermatitis

Dermatitis Medicamentosa, Fixed Type, from Arsenicals

Dermatitis Medicamentosa Due to Neoarsphenamine

Hydroa Vacciniformis in a Boy Aged 13 Years

Sarcoidosis? Tuberculosis in a Negro?

Severe Hypoplastic Anemia Following Arsenical Therapy

A Case for Diagnosis (Lupus Erythematosus? Pigmented Nevus?) Presented by DR GEORGE B SEXTON, London, Ontario, Canada

Neurocutaneous Leprosy, Originating in a Tattoo Presented by DR CLAUDE BEHN and (by invitation) DR ROSS J PORRITT

L G, a white man, was first seen on Nov 11, 1946, complaining of a cutaneous lesion involving a tattoo and the surrounding area on the flexure surface of the left forearm and also two areas forming an hourglass shape on the extensor surface of the middle third of the left arm

In June 1943 while a member of the United States Medical Corps, he was tattooed in Melbourne, Australia Three years later he first noticed increased pigmentation and loss of superficial sensation involving the tattoo and the surrounding area In a friend who was tattooed at the same time by the same person a similar lesion developed

The skin of the entire tattoo and a zone 15 cm in width about it shows a violaceous discoloration There is a loss of pain and light touch sensation throughout the entire pigmented area On the extensor surface of the left arm, 75 cm above the elbow, there are two coalescent lesions making an hourglass-shaped area 25 by 4 cm This has the same violaceous color as the tattoo area, and there is the same loss of sensation There is no ulceration or elevation present and no palpable abnormality of the nerve trunks

The reaction to intradermal injections of old tuberculin, 0.1 cc in a dilution of 1 to 10,000, was negative The Kahn reaction was negative The blood and urine were normal Guinea pig inoculation with tissue gave a negative result

The skin and subcutaneous tissue show a tuberculoid reaction There appears to be slight caseation in centers of some of the nodules Fairly numerous well developed Langhans giant cells are present The nodules extend through the corium into the subcutaneous fat Occasional acid-fast bacilli were found by the Ziehl-Neelsen stain They averaged not more than 1 per section

DISCUSSION

DR FRANK MENAGH How was the leprosy transmitted?

DR. ROSS J PORRITT (by invitation) It may be that the operator licked the needle

DR FRANK MENAGH How about excising the area?

DR ROSS J PORRITT (by invitation) We discussed the possibility of excising it, but, considering the spread up above the elbow, we did not think it advisable We did recommend that the boy go to Carville for six months, although the Health Department will not force him to go as long as there are no open lesions Treatment with one of the new sulfone drugs may be tried

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